Medical Library
JUN 20 1944

INDEX NUMBER

Vol. 207, No. 6 JUNE, 1944 No. 867

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

REG. U. S. PAT. OFF.

Editor:
E. B. KRUMBHAAR, M.D.

Acting Assistant Editor:
WILLIAM C. STADIE, M.D.

Established 1820

THIOURACIL STORAGE IN THE THYROID AS AFFECTED BY THYROTROPIC HORMONE AND POTASSIUM IODIDE. By ROBERT H. WILLIAMS, M.D., ALBERT R. WEINGLASS, M.D., and GLORIA A. KAY. 701

INTERFERENCE BETWEEN INACTIVE AND ACTIVE VIRUSES OF INFLUENZA. I. THE INCIDENTAL OCCURRENCE AND ARTIFICIAL INDUCTION OF THE PHENOMENON. By WERNER HENLE, M.D., and GERTRUDE HENLE, M.D. 705

INTERFERENCE BETWEEN INACTIVE AND ACTIVE VIRUSES OF INFLUENZA. II. FACTORS INFLUENCING THE PHENOMENON. By WERNER HENLE, M.D., and GERTRUDE HENLE, M.D. 717

ONE YEAR OBSERVATIONS OF THE TREATMENT OF CANCER WITH AVIDIN (EGG WHITE). By IRA I. KAPLAN, B.S., M.D. 733

CONCENTRATION OF RED BLOOD CORPUSCLES CONTAINING LABELED PHOSPHORUS COMPOUNDS IN THE ARTERIAL BLOOD AFTER THE INTRAVENOUS INJECTION. PRELIMINARY REPORT. By GUSTAV NYLIN and MIGNON MALM. 743

THE EVALUATION OF ALCOHOL LUMBAR PARAVERTEBRAL BLOCK IN PERIPHERAL VASCULAR DISEASE. By GAMLIEL SALAND, M.D., and CAPT. CHARLES KLEIN, M.C., A.U.S. 749

AMEBIASIS: ANALYTICAL STUDY OF THE CASES ADMITTED TO A PHILADELPHIA HOSPITAL DURING THE LAST 5 DECADES. By R. S. DIAZ-RIVERA, M.D., and EDWIN A. RASPBERRY, M.D. 754

TRICHINELLA SKIN TESTS IN PATIENTS IN GENERAL HOSPITALS AND TUBERCULOSIS SANATORIA. By S. F. HORNE, M.D., and GEORGE T. HARRELL, M.D. 759

HEART BLOCK. A STUDY OF 100 CASES WITH PROLONGED P-R INTERVAL. By ROBERT BRUCE LOGUE, Major, M.C., A.U.S., and JAMES FLETCHER HANSON, Major, M.C., A.U.S. 765

NEUROPSYCHIATRIC CASUALTIES FROM GUADALCANAL. I. PERSISTENT SYMPTOMS IN 3 CASES. By MAJOR ALBERT A. ROSNER, M.C., A.U.S. 770

TUMEFACTION OF SUBCUTANEOUS FAT FOLLOWING THE INJECTION OF INSULIN. A CHEMICAL AND HISTOLOGIC STUDY. By HUGO T. ENGELHARDT, M.D., and VINCENT J. DERBES, M.D. 776

PROGRESS OF MEDICAL SCIENCE:

PEDIATRICS: MAJOR MOTILITY PATTERNS OF THE CHILD'S DIGESTIVE TRACT: A REVIEW. By IRVING J. WOLMAN, M.D. 782

GYNECOLOGY AND OBSTETRICS: ANALGESIA IN OBSTETRICS. By JAMES F. DONNELLY, M.D. 804

PROCEEDINGS OF THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA . . . 812

Contents continued on adv. page 10

OWNERS AND PUBLISHERS LEA & FEBIGER PHILADELPHIA 6, PENNA.

COPYRIGHT, 1944, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER

PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR

Lowering blood pressure of hypertensive patients must be done safely to avert fatalities. Sustained effect and low toxicity should characterize the medication employed, qualities difficult to achieve with the nitrites and barbiturates respectively.

HEPVISC has proved a valuable hypotensive, with extensive clinical use. Not only does it bring blood pressure down in a gradual manner, but its effect is sustained. Striking relief of hypertensive symptoms such as headaches, dizziness and tinnitus also ensue with the administration of **HEPVISC** in well over 80% of cases.

Each **HEPVISC** Tablet contains Viscum album extract 50 mg., hepatic desiccated substance 60 mg. and insulin-free pancreatic desiccated substance 60 mg.

INDICATIONS: Essential hypertension, benign hyperpiesia, fibrotic kidney and hypertension accompanying pregnancy.

DOSAGE: Average dose is 3 to 6 tablets daily, in divided doses ½ hour before meals. Continue treatment for 2 to 3 weeks with a week's interval between courses.

Bottles of 50 and 500 tablets.

Liberal samples to physicians on request.

HEPVISC

AN EFFECTIVE HYPOTENSIVE

ANGLO-FRENCH LABORATORIES, INC.

75 VARICK STREET, NEW YORK 13, N. Y.

THE AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JUNE, 1944

ORIGINAL ARTICLES

THIOURACIL STORAGE IN THE THYROID AS AFFECTED BY THYROTROPIC HORMONE AND POTASSIUM IODIDE

By Robert H. Williams, M.D.

INSTRUCTOR IN MEDICINE, HARVARD MEDICAL SCHOOL; ASSISTANT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY; JUNIOR VISITING PHYSICIAN, BOSTON CITY HOSPITAL

Albert R. Weinglass, M.D.

RESEARCH FELLOW, HARVARD MEDICAL SCHOOL; RESEARCH FELLOW, THORNDIKE MEMORIAL LABORATORY; ASSISTANT IN MEDICINE, BOSTON CITY HOSPITAL

AND

Gloria A. Kay

LABORATORY ASSISTANT, THORNDIKE MEMORIAL LABORATORY
BOSTON, MASS.

Thiouracil has recently been used in the treatment of thyrotoxicosis.[1,3] It leads to a fall in the basal oxygen consumption to normal levels with an associated clinical improvement and a decrease in the protein bound iodine content of the plasma. The effectiveness of this drug in inducing the foregoing changes is due to its inhibitory action on the production of the thyroid hormone. Therefore, the amount of thiouracil stored in the thyroid is of importance.

Using the method of Williams, Jandorf and Kay,[4] the content of thiouracil in the thyroid glands of thyrotoxic patients treated with thiouracil has been determined for varying intervals. These values have been compared with those obtained in "normal" glands.[5] The latter values were obtained by administering thiouracil to patients without thyroid disease but with a hopeless prognosis, and estimating the amount of the drug in the thyroid gland at postmortem. However, the variability in the pathologic processes in each group makes it desirable to study this subject under better controlled conditions. Guinea pigs were selected for a continuation of these investigations. These animals were also used for a study of the effect of iodide treatment on the storage of thiouracil in the thyroid.

Method. All thiouracil* was administered as 0.25% solution in the form of its sodium salt at a pH of 8. No other drinking water was given. Thyrotropic hormone* was injected subcutaneously in daily doses of 0.1 cc., the last

* We are indebted to the Lederle Laboratories, Inc., Pearl River, N. Y., for the supply of thiouracil and to Parke Davis & Co., Detroit, Mich., for the thyrotropic hormone (Antuitrin T). Each cc. of this hormone contains approximately 50 Junkmann-Schöller units.

injection being given 24 hours before the animal was killed. The guinea pigs receiving iodide therapy were given potassium iodide in the form of an aqueous solution containing 50 mg. per 100 cc. When iodide was given with the thiouracil, the two substances were given in one solution in the same concentrations as above. The animals were killed by means of a blow on the head. The thyroid gland was dissected out, weighed on a microbalance, minced, placed in about an equal volume of 1 N sodium hydroxide and then analyzed for the thiouracil content according to the method of Williams, Jandorf and Kay.[4]

Five series of animals were studied as follows:

Series No. 1. Five guinea pigs weighing from 416 to 555 gm. were given thiouracil for 6 days. Two of these animals were also injected with thyrotropic hormone for 7 days, beginning 1 day before the thiouracil treatment.

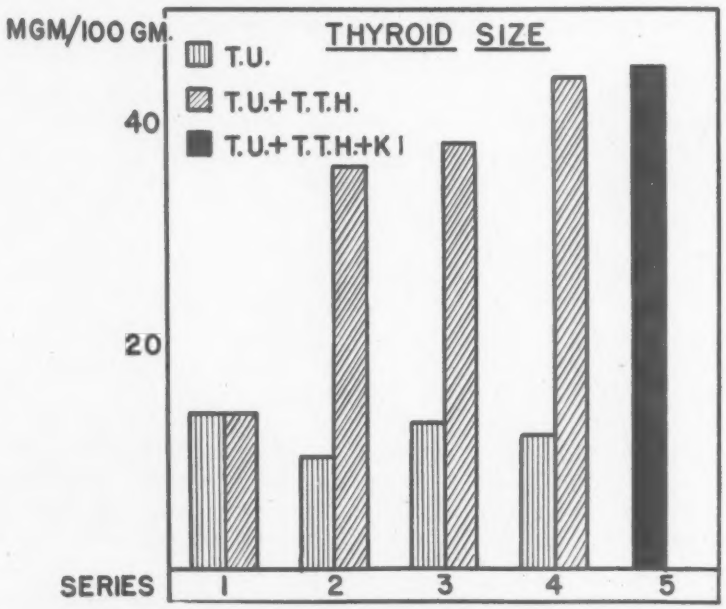


FIG. 1.—Effect of thiouracil (T.U.), thyrotropic hormone (T.T.H.) and potassium iodide (KI) on the average size of the thyroid expressed in terms of wet weight per 100 gm. body weight. The series numbers are explained in the text.

Series No. 2. Six animals, 5 weighing from 414 to 506 gm. and 1 weighing 249 gm., were given thiouracil for 4 days. Three of these animals were also given thyrotropic hormone for 5 days.

Series No. 3. Eleven animals, weighing from 204 to 253 gm., were given thiouracil for 5 days; 6 were also given thyrotropic hormone for 6 days.

Series No. 4. Six guinea pigs, 5 weighing from 321 to 375 gm. and 1 weighing 475 gm., were given thiouracil for 10 days. Three of these were also given thyrotropic hormone for 11 days.

Series No. 5. Six animals, weighing from 300 to 510 gm., were given thyrotropic hormone for 11 days, potassium iodide for 9 days and thiouracil for 5 days.

In each series the thyrotropic hormone therapy was started 1 day before any other treatment because it was our purpose to have the animals in a hyperthyroid state when thiouracil or iodide was given. The experiment dealing with the pigs in Series No. 5 was designed to be somewhat comparable to thyrotoxic patients treated first with iodide and then thiouracil.

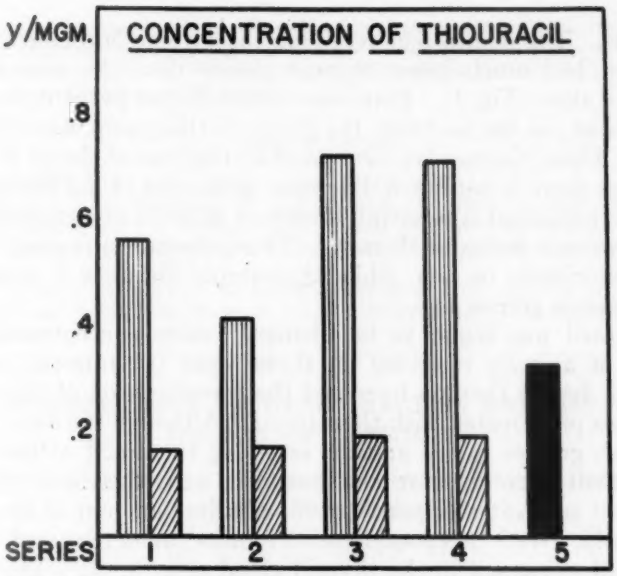


FIG. 2.—Effect of thyrotropin and potassium iodide upon the average concentration of thiouracil in the thyroid gland. Symbols as in Figure 1.

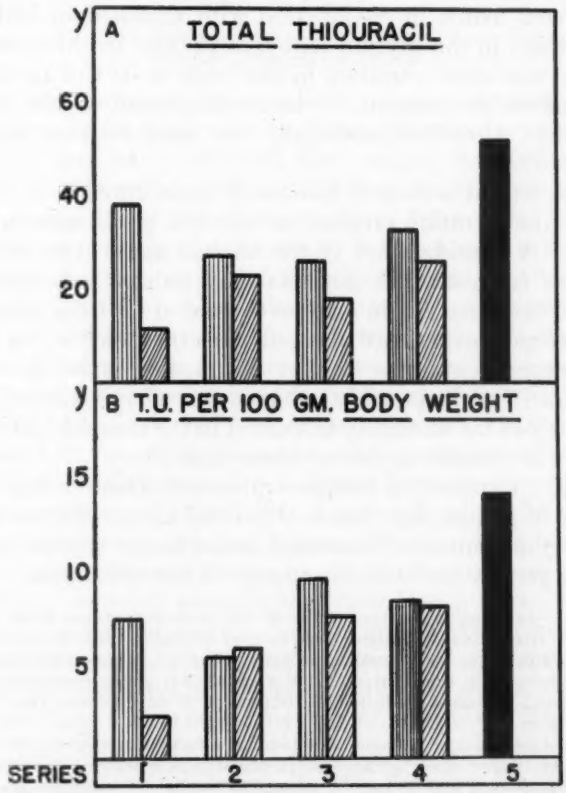


FIG. 3.—*A*, Average total thiouracil in each thyroid gland. *B*, Average content of thiouracil in thyroid per 100 gm. of body weight. Symbols as in Figure 1.

Results. The guinea pigs receiving thyrotropic hormone as well as thiouracil had much larger thyroid glands than the ones receiving thiouracil alone (Fig. 1). Potassium iodide did not prevent the thyroid enlargement; on the contrary, the glands in this group were the largest of any. These changes are more marked than are observed in the rat. In the rat there is not much difference in the size of the thyroid gland whether the animal is receiving thiouracil alone or in conjunction with the thyrotropic hormone therapy.[6] This is because thiouracil is much more goiterigenic in rats, while thyrotropic hormone is much more goiterigenic in guinea pigs.

Thiouracil was found to be distinctly more concentrated in the thyroid of animals receiving no thyrotropin (thyrotropic hormone) (Fig. 2). Iodide therapy increased the concentration of thiouracil in the guinea pigs treated with thyrotropin. Although the concentration was much greater in the animals receiving thiouracil without thyrotropin, their thyroids were much smaller, and, therefore, one would not expect so great a disparity in the absolute amount of the drug in the thyroid. With this consideration in mind we determined the total amount of thiouracil in the thyroid gland (Fig. 3, *A*). The animals receiving no thyrotropic hormone were found to have a larger amount in the whole gland than the ones receiving the hormone. However, the pigs given iodide in conjunction with thyrotropin had distinctly more thiouracil in the thyroid than was present in either other group. Since there was some variation in the body weight of the animals we have calculated the amount of thiouracil present on the basis of the body weight. However, essentially the same relative changes were found (Fig. 3, *B*).

Since the site of action of thiouracil is presumably in the thyroid gland, the concentration attained at this site would seem to be highly important. A consideration of the clinical application of the above observations suggests that patients may require a larger dosage of thiouracil when they are in a hyperthyroid state than when they are not. Our clinical experience also indicates that such is the case. The foregoing experiments also suggest that iodide given in conjunction with thiouracil might possibly enhance the effectiveness of the latter since it increases the storage of thiouracil in the thyroid. At the present time we are investigating this problem clinically.

Summary. Thyrotropic hormone given with thiouracil is much more goiterigenic in guinea pigs than is thiouracil alone. Thyrotropin tends to decrease the amount of thiouracil stored in the thyroid while potassium iodide greatly increases the storage of this substance.

ADDENDUM: In interpreting the results of our experiments, one must bear in mind the possibility that thiouracil might have formed a combination with iodine either in the drinking water, since both compounds were in one solution, or that these substances might have combined in the thyroid. It is known[2] that iodine reacts with thiourea to form formamidine disulfide hydroiodide, but there is no evidence that this reaction occurs in the body.

In order to study certain biologic and chemical effects of a mixture of thiouracil and iodide we administered these substances in the drinking water to guinea pigs, using 0.25 per cent thiouracil and 50 mg. % potassium iodide. To another group of guinea pigs we gave the same amount of thiouracil but no iodide. At the end of 10 days the

stock solutions contained the same concentration of thiouracil. At this time there was essentially no difference in the 2 groups of animals as concerned the size of the thyroid, the histologic structure, the concentration of thiouracil in the thyroid gland and the total amount of this drug in the thyroid.

REFERENCES

1. Astwood, E. B.: J. Am. Med. Assn., **122**, 78, 1943.
2. Baumann, E. J., Metzger, N., and Marine, D.: Endocrinology, **34**, 44, 1944.
3. Williams, R. H., and Bissell, G. W.: New England J. Med., **229**, 97, 1943.
4. Williams, R. H., Jandorf, B. J., and Kay, G. A.: J. Lab. and Clin. Med., **29**, 329, 1944.
5. Williams, R. H., Kay, G. A., and Jandorf, B. J.: (In press.)
6. Williams, R. H., Weinglass, A. R., and Peters, J. B.: (In preparation.)

INTERFERENCE BETWEEN INACTIVE AND ACTIVE VIRUSES OF INFLUENZA*

I. The Incidental Occurrence and Artificial Induction of the Phenomenon

By Werner Henle, M.D.
and
Gertrude Henle, M.D.
Philadelphia, Pa.

(From the Department of Pediatrics, School of Medicine, Univ. of Pennsylvania, and the Children's Hospital of Philadelphia.)

Interference of one active virus with the propagation of another in mutually susceptible host cells has been described repeatedly. This phenomenon has been observed first among phytopathogenic viruses.[16,18,24] Although suggestive evidence of its occurrence among animal viruses may be drawn in retrospect from earlier publications, interference was clearly demonstrated first between neurotropic and viscerotropic strains of yellow fever virus by Hoskins[14] and between encephalitogenic and non-encephalitogenic herpes virus by Magrassi and others.[7,19] The phenomenon does occur not only among viruses as closely related as those mentioned—and as additional examples may be cited interference between various strains of poliomyelitis virus[15] and between biologically distinct strains of influenza virus[3]—but interference has been noted also between agents serologically quite unrelated. Thus Findlay and MacCallum[8] have observed interference between the viruses of Rift Valley fever and yellow fever. Dalldorf and Douglass[5] demonstrated a "sparing effect" of lymphocytic choriomeningitis infection in monkeys on superinfection with the virus of poliomyelitis. Similar observations have been made with various serologically unrelated animal viruses and bacteriophages.[2,6,9,17,21,25] This apparent non-specificity, together with the rapidity with which protection by interference could be obtained, set this phenomenon quite apart from immunologic reactions. However, interference has

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Children's Hospital of Philadelphia.

been noted only between certain viruses and not between others, perhaps signifying biologic relationship, and examples have been reported of typical inclusions due to two different viruses in a single host cell,[1,22] although in different structures (nucleus and protoplasm).

The data obtained in interference of two active agents permit many explanations. One would have to think of hindrance of spread of the second virus infection due to pathologic changes in the host caused by the first. Taylor and Sprunt[23] have shown that increased tissue fluid may hinder the spreading of vaccinial infection in the skin of rabbits. One might consider virucidal properties of either the interfering virus or of abnormal metabolic products of the infected host cell. Greater avidity of one virus for certain essential nutrients or enzyme systems appears as another possible explanation. Finally, a blockade of "cell receptors" has been assumed. Not every one of the suggested explanations can account for all the observed facts, and, on the other hand, it is conceivable that interference may be caused by different mechanisms in the various instances.

A new aspect of the problem was introduced by Luria and Delbrück[17] when they noted that bacteriophage inactivated by ultra-violet irradiation still produced interference not only with a heterologous strain of active virus but also with the homologous agent. Studying this system, the authors concluded that the interfering agents compete for some key material within the host cell, possibly an enzyme. How far these data are applicable to animal viruses remains to be seen. However, it has been shown that irradiated influenza virus interferes with the propagation of the active agent in the allantoic sac of the chick embryo,[11] and Jungeblut and Sanders make brief mention of a similar observation with the virus of poliomyelitis in mice, for which experimental data have not yet been published.[15]

It is the aim of this series of publications to study the interference phenomenon produced by inactivated influenza virus from various points of view. The present communication is an extension of the preliminary paper,[11] demonstrating the phenomenon as it occurs incidentally or following artificial inactivation of influenza virus. This study was greatly aided by the recent observation of Hirst,[13] who found that preparations of active and inactivated influenza viruses agglutinate chick red blood cells. This hemagglutination reaction can be utilized for the rapid and quantitative determination of virus multiplication.

Methods and Materials. *Virus.* Embryonated eggs at the 10th day of incubation were inoculated by the allantoic route[10] with 0.5 ml. of virus suspension suitably diluted in buffered saline solution of pH 7.0. The PR–8 and WS strains of influenza A and the Lee strain of influenza B virus were mostly employed. After sealing the hole in the shell above the air sac through which the injection was made, the eggs were incubated at 36° to 37° C. for varying periods of time as indicated in the text. Mortality of the embryos at this temperature due to influenza was usually negligible regardless of the concentration of the inoculum. At the end of the incubationary period the eggs were chilled at −10° to −15° C. for 30 to 60 minutes, or at 4° C. for 2 to 4 hours to prevent bleeding during harvest of the allantoic fluids. Each experimental group consisted of at least 8 to 10 eggs, and the fluids harvested from each were

either pooled directly or, in later experiments, samples of individual fluids were kept for separate study and equal amounts of each fluid were pooled. Adequate samples of the various pools were stored immediately after harvest in sealed ampules at −70° C. until titration for virus activity in mice or chick embryos was possible, and for eventual repetition of doubtful results.

Large batches of allantoic fluid for irradiation or for standard test virus to be kept at −70° C. were harvested by a suction device (Fig. 1). It consists of a 10 ml. volumetric pipette with closed tip and an opening at its side. The pipette is bent in the manner indicated to permit easier operation, and inserted through a rubber stopper fitting into suitable bottles. One arm of a glass T-piece is inserted through another hole in the stopper, the horizontal arm is connected by light rubber tubing to an aspirator operating at a negative pressure of approximately −2 cm. Hg, and the third arm, extending vertically, is left open. The flask is grasped around the neck so that the index finger may conveniently reach the open end of the T-piece. While idling, the air

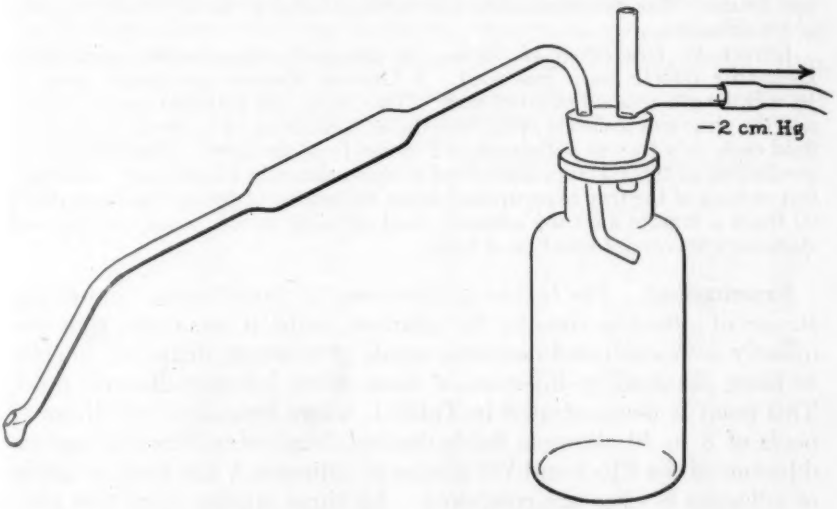


FIG. 1.—Suction device for the harvest of allantoic fluid.

passes from the open end of the T-piece directly to the aspirator without entering the flask. After the tip of the pipette is introduced into the allantoic cavity, its opening is directed towards the inside wall of the egg. The glass drop at the tip is designed to keep tissues away. The free end of the T-piece is closed with the index finger and the allantoic fluid is aspirated into the pipette. The bulb is required to slow down the flow, and in case of rupture of the yolk sac or admixture of blood, release of the index finger will stop suction immediately and the unwanted fluid runs back into the egg. The pipette may be washed with sterile saline solution by repeated aspiration and release before resuming the harvest. Large batches of allantoic fluid (200 to 600 ml.) have been collected with one pipette by this method without bacterial contamination.

Virus Titration in Mice. Serial ten-fold dilutions of the allantoic fluid were made in sterile broth and 4 to 6 white mice each inoculated intranasally under light ether anesthesia with 0.05 ml. of the different dilutions. The mice were 3 to 4 weeks of age and weighed between 12 and 15 gm. Animals found dead during the experimental period were examined for typical lesions. Surviving mice were sacrificed on the 10th day and the degree of pulmonary involvement recorded as 4 = lungs totally consolidated; 3 = ¾ of lungs consolidated; 2 = ½ of the lungs; 1 = ¼ of the lungs; ± = less than ¼ consolidated; and

0 = no visible lesions. The 50% mortality end-point (LD_{50}) was calculated according to the method of Reed and Muench.

Agglutination of Chick Red Cells. The technique described by Hirst was used.[13] Serial two-fold dilutions of the infected allantoic fluids were made in saline solution and an equal amount (1 ml.) of a 2% suspension of thrice-washed chick red cells added by an automatic pipette. The degree of sedimentation of red cells was recorded after 75 minutes at room temperature by determining the percentage of red cells left in suspension with the aid of a photo-electric densitometer. The end-point was arbitrarily chosen as the final dilution of allantoic fluid in which enough red cells were left in the supernatant fluid to correspond to a 0.63 to 0.5% suspension. In case the transition from a negative reading to a strongly positive sedimentation occurred from one tube to another, the titer was considered to be halfway between these two dilutions. In all experiments, at least two determinations of the agglutinative titer were carried out on two different days with chick cells not older than 3 days. In all cases the average titer was computed and recorded in the tables and figures. The determinations were always found to agree within one step of the dilutions.

Ultra-violet Irradiation of Virus. In the early experiments, a Hanovia Examalite quartz lamp was used. A General Electric germicidal lamp of 18 inch length was substituted later. This lamp was installed under a hood and the virus was placed in open Petri dishes containing 15 to 18 ml. of allantoic fluid each on a tray at a distance of 7 inches from the lamp. The intensity of irradiation at this distance amounted to approximately 275μW/cm^2. Mechanical rocking of the tray in an up-and-down movement of about 1 inch excursion 90 times a minute kept the allantoic fluid agitated in such a way as to avoid stationary waves or formation of foam.

Experimental. *The Incidental Occurrence of Interference.* In passing strains of influenza virus by the allantoic route, it was noted that frequently a concentrated inoculum would give results distinctly inferior to those obtained by injection of more dilute infected allantoic fluid. This point is demonstrated in Table 1, where hemagglutinin titers of pools of 8 to 10 allantoic fluids derived from subcultures in various dilutions of the PR–8 and WS strains of influenza A and the Lee strain of influenza B virus are compared. All three strains show this phenomenon to some extent, although not regularly. Three additional strains of influenza A virus, not represented in the table, have yielded similar results. This inhibitory effect is particularly marked with the Lee strain of influenza B virus, in which case sometimes no or only low agglutinative titers were recorded in allantoic fluids derived from concentrated inocula, while more dilute seed produced the usual high titers. As will be shown later, the low titers encountered in subcultures of undiluted infected allantoic fluid may be due to residual hemagglutinins from the inoculation rather than the result of virus propagation.

In the experiments cited in Table 1, all fluids of one series were harvested after the same period of incubation, usually after 48 hours. It was conceivable that fluids derived from concentrated inocula may have had a higher hemagglutinin titer at an earlier stage of the incubationary period, with subsequent loss of activity on further incubation. However, this could not be verified as inspection of Figure 2 will show. The figure summarizes two experiments conducted either with influenza A (PR–8) or with B virus (Lee). When the allantoic fluids of groups of eggs inoculated with different concentrations of virus

were collected after various times of incubation, it was found that the agglutinative titers of allantoic fluids derived from concentrated inocula were lower throughout the series of fluids than those obtained from fluids following injection of dilute virus. While the agglutinative titer after reaching its maximum remains more or less constant for several days of incubation, the infectivity of the allantoic fluids as measured by inoculation of mice falls off after attaining its peak. Similar observations have been made by Burnet with the Melbourne strain of influenza A.[4] The height of this peak, like that of the hemagglutinin titer, depends on the concentration of the inoculum, and under optimal conditions 100 to 300 times more active virus was obtained from dilute inocula than from concentrated ones. Maximal concentration of active virus and hemagglutinins for the various conditions was reached earlier following injections of more concentrated virus, and correspondingly later when dilute virus was employed. It is to be noted that the peak of active virus is reached earlier than the maximal hemagglutinin titer.

TABLE 1.—RELATION BETWEEN CONCENTRATION OF SEED CULTURE AND TITER OF HEMAGGLUTININS IN SUBCULTURE

Derivation of seed culture			Hemaggl. titer of subculture inoculated with seed culture in dilution				
Strain	Prepared from dilution	Time of incubation (hours)	10^{0}	10^{-1}	10^{-2}	10^{-3}	10^{-4}
PR-8	10^{-5}	48	620	556	512	640	n.t.
	10^{-4}	24	256	192	384	384	384
	10^{-4}	96	192	128	192	384	512
	10^{-1}	48	n.t.	80	n.t.	320	n.t.
	10^{-1}	48	192	128	320	768	768
WS	10^{-4}	24	96	224	448	1024	768
	10^{-4}	96	144	192	256	768	640
	10^{-4}	96	32	128	256	n.t.	1024
	10^{-3}	48	n.t.	64	256	512	n.t.
	10^{-1}	48	n.t.	112	512	768	n.t.
	10^{-1}	48	40	112	384	384	512
Lee	10^{-4}	48	128	224	256	300	320
	10^{-3}	72	96	112	64	256	512
	10^{-2}	36	64	32	32	64	256
	10^{-2}	96	12	<2	32	224	<2
	10^{0}	48 + 72	3	48	192	512	n.t.
	10^{0}	24	16	24	4	24	192

n.t. = not tested.

The impression was gained, and Table 1 shows it to some extent, that the inhibitory property of concentrated inocula was more likely to be found in allantoic fluids which were harvested after an extended period of incubation, that is, after the infectivity had decreased. This effect, as pointed out, would occur earlier following inoculation of low dilutions of allantoic fluids than when high dilutions were injected (compare Fig. 2). Similar observations were reported recently by Miller.[20] In addition, handling of the virus between passages, *i. e.*, the temperature of storage, repeated freezing and thawing, etc., seemed to play a rôle in the production of the phenomenon. These clues suggested that the possible presence of inactive virus in the seed might interfere with the propagation of the active agent. To test this possibility, attempts were made to increase the amount of inactive virus in infected allantoic fluids artificially, and the results of subcultures from partially inactivated preparations were found in agreement with the assumption.

Artificial Production of Interference. Experiments on the injection of eggs with virus partially inactivated either by heating to 56° C. or by irradiation with ultra-violet light are summarized in Table 2. The PR–8 virus in allantoic fluid was heated at 56° C. in individual test tubes, and one tube each removed from the water bath at the indicated time. The original infected allantoic fluid had no inhibitory effect. After five minutes of incubation at 56° C., formation of hemagglutinins following injection of undiluted fluid reached a titer of only 1:32, while 1000-fold diluted seed produced a titer of 1:1024. Heating for 10

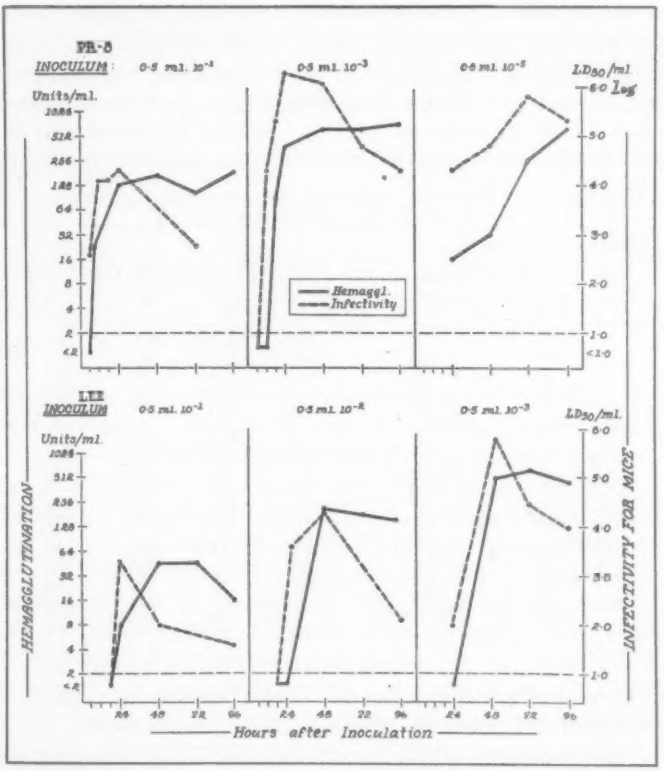


FIG. 2.—Development of active virus and hemagglutinins following inoculation of various concentrations of seed culture.

minutes produced even more striking results in that the undiluted inoculum produced no measurable hemagglutinins while a 100-fold diluted inoculum of the same heated fluid gave a high titer. Similar results were obtained after ultra-violet irradiation of the WS strain of influenza A virus. The non-irradiated preparation showed some inhibition, but the effect could be markedly increased by irradiation for 2 minutes, and with 10 minutes' irradiation the results were very similar to those obtained with the PR–8 strain by heating to 56° C. for 10 minutes. It is to be noted that the hemagglutinin titer of the inoculum was definitely affected by heating, since it decreased from

1:512 in the original fluid to 1:192 after 30 minutes at 56° C., and after 60 minutes frequently only 20% or less of the original titer was left. The ultra-violet irradiation of the allantoic fluid did not have this effect under the conditions of the experiment, and the titer stayed constant for the duration of the exposure. Different results were obtained after irradiation of dialyzed allantoic fluids or with exposure to stronger irradiation, as will be shown later.

TABLE 2.—EFFECT OF HEAT AND ULTRA-VIOLET IRRADIATION ON INHIBITORY PROPERTY OF CONCENTRATED INOCULA

Inoculum				Hemagglutinin titer of subculture inoculated in dilution				
Strain of virus	Means of inactivation	Time of inactivation (min.)	Hemagglutinin titer	10^{0}	10^{-1}	10^{-2}	10^{-3}	10^{-4}
PR-8	Heat (56° C.)	0	512	620	600	512	640	n.t.
		5	256	32	112	640	1024	n.t.
		10	256	<2	224	1024	<2	n.t.
		20	192	12*	320	256*	<2	n.t.
		30	192	<2	24*	<2	<2	n.t.
WS	Ultra-violet irradiation	0	512	96	224	448	1024	768
		2	512	48	80	256	768	256
		5	512	8	8	80	512	256
		10	512	<2	8	80	512	1024
		20	512	6	24	256	448	n.t.
		30	512	<2	40	448	n.t.	n.t.

* One or 2 out of 6 allantoic fluids positive.
n.t. = not tested.

The experiments reported thus far indicated that inactive virus accumulating under certain conditions in the allantoic fluid, or artificially increased by heating or irradiation of the infectious materials, when injected into the allantoic cavity of the chick embryo, interfered with the propagation of the active agent present in the same preparations. Thus, protection of susceptible cells was obtained rapidly, and the possible value of this phenomenon in prevention of influenzal infections suggested further investigations. It was obvious that the foregoing set-up did not permit quantitative estimations and analysis of the relationships between active and inactivated virus. Attempts were made, therefore, to produce on the one hand fully inactivated virus with the interfering property largely intact, and to test for the interfering property with known amounts of the active agent. The following experiments were designed to lead towards this goal.

Infected allantoic fluids irradiated for as long as 60 minutes were usually not completely inactive. Although a single subculture of such fluids in mice or chick embryos frequently did not disclose signs of infection, a second passage often did. By these means it was shown that allantoic fluid from the first passage contained, on occasion, as much as 10,000 LD_{50} for mice per milliliter, without having revealed agglutination of chick red cells. In other instances only very little virus was demonstrable by second passage. In spite of this incomplete inactivation of virus, experiments were conducted to test whether injection of active virus either at the time of or following the inoculation of irradiated fluids would prevent the propagation of the virus. The results of some of these experiments are summarized in Table 3. In all instances groups of eggs were inoculated with 0.5 ml. amounts of

either irradiated infected or normal allantoic fluid. Those injected with the infected material were subsequently tested with either active virus or saline solution (0.2 ml.), while those receiving normal fluid were tested only with virus. After further incubation of 48 hours, the allantoic fluids were collected and tested for agglutination of chick red cells and infectivity for mice. As can be seen in the table, inoculation of irradiated virus into the allantoic cavity usually did not of itself produce measurable amounts of hemagglutinin. Secondary injection of active virus into eggs primarily inoculated with irradiated virus did not alter the results, and no agglutination of red cells was obtained with the allantoic fluids harvested from these eggs. Titration of these fluids in mice, however, revealed measurable amounts of active virus, regardless of whether the eggs were secondarily injected with active virus or saline, and the LD_{50} frequently did not differ significantly between the two groups. These titers, however, were markedly lower than those obtained with fluids derived from eggs tested with active virus following injection of normal fluid. In this latter case the fluids contained as much as 1000 to 10,000 times the amount of active virus in addition to high hemagglutinin titers. These results did not differ very much, regardless of whether the test virus was injected simultaneously with, or 3 to 24 hours following the injection of the irradiated material. Only homologous interference reactions are shown in Table 3. Cross-interference has been noted between various strains of influenza A, and between influenza A, B, and swine virus. These tests will be discussed in a subsequent paper.

TABLE 3.—SUMMARY OF INTERFERENCE EXPERIMENTS WITH NON-DIALYZED ALLANTOIC FLUIDS IRRADIATED WITH ULTRA-VIOLET LIGHT

	First injection			Second injection				
					Saline solution		Active virus	
Experiment	Strain of virus	Time of ultra-violet irrad. (min.)	Infectivity for mice	Time after 1st injection (hours)	Hemagglutinin titer	LD_{50} in mice	Hemagglutinin titer	LD_{50} in mice
1.	WS (24 hr.)*	30	321000	0	<2	n.t.	<2	n.t.
				3	<2	$10^{4.0}$	<2	$10^{4.3}$
	WS (96 hr.)	30	±000	0	<2	n.t.	<2	$10^{2.3}$
				3	<2	$10^{2.3}$	<2	$10^{2.8}$
	Normal all. fluid	..	..	..	..	..	768	$10^{6.8}$
2.	WS (96 hr.)	30	n.t.	3	3	$10^{1.3}$	3	$10^{2.3}$
				24	<2	n.t.	<2	n.t.
	Normal all. fluid	..	n.t.	3	..	..	256	$10^{5.3}$
3.	WS (72 hr.)	60	000000	3	<2	$<10^{1.3}$	<2	$10^{2.5}$
	Normal all. fluid	60	000000	3	..	..	384	$10^{5.6}$
4.	Lee (96 hr.)	30	n.t.	0	..	n.t.	8	$10^{2.1}$
	Normal all. fluid	30	..	0	..	n.t.	288	$10^{4.2}$

* (24 hr.) = incubationary period of virus used for irradiation.

It could be shown that the hemagglutinin formation was not simply delayed by the injection of irradiated virus previous to active virus, since the results were similar whether the allantoic fluids were harvested 48 or 96 hours after the test virus injection (see Table 4).

The table also shows that the results in individual eggs are usually quite uniform. In the experiment cited, only 3 out of 16 allantoic fluids of the experimental group showed a minimal amount of hemagglutinins. Of the 8 control eggs, all showed strong agglutination of chick red cells in dilution of 1:200, and the pool of these fluids gave a titer of 1:512. This uniformity, however, did not always occur. On occasion, one or the other of the saline controls showed a fairly high titer of hemagglutinins, while the remainder revealed no measurable quantities. These irregularities have not been satisfactorily explained. In other instances 1 or 2 out of 10 eggs tested with active virus following irradiated virus showed a high titer, while the others, as well as the controls tested with saline solution, did not. It is considered probable that the injection of irradiated virus in these cases may not have entered the allantoic cavity at all, or only partly, thereby preventing or reducing interfering activity. Because these failures occurred, it was necessary in all experiments of this type to harvest the allantoic fluids individually and to pool equal amounts of each group for testing. This made it possible to study the regularity of the interference phenomenon and to check back in case of irregularities.

TABLE 4.—RESULTS OF INTERFERENCE AFTER 48 AND 96 HOURS OF INCUBATION

			Hemagglutinin titer following second injection of active virus								
			Number of chick embryo								
First injection	Time of harvest (hours)	Dilution of allantoic fluid	1	2	3	4	5	6	7	8	Titer of pooled allantoic fluids
Irradiated virus	48	1:2	±	−	±	−	−	−	−	−	<2
		1:20	−	−	−	−	−	−	−	−	
	96	1:2	−	+	−	−	−	−	−	−	<2
		1:20	−	−	−	−	−	−	−	−	
Irradiated normal allantoic fluid	48	1:2	++	++	++	++	++	++	++	++	512
		1:20	++	++	++	++	++	++	++	++	
		1:200	++	++	++	++	++	++	++	++	

++ indicates more than 63% of red cells sedimented; + between 50 and 63%; ± between 37 and 50% of red cells sedimented.

Effect of Dialysis of Allantoic Fluid on Inactivation of Virus by Irradiation. Although these results further confirmed the occurrence of interference between active and inactive influenza virus, the value of the tests was diminished by the presence of relatively large amounts of active virus both in the experimental and control groups. This was due to incomplete inactivation of the agent in straight allantoic fluid by ultra-violet irradiation. An improvement was noted when allantoic fluids were dialyzed against buffered saline solution before exposure to the ultra-violet rays. Since the fluids contain relatively large and variable amounts of urates which absorb ultra-violet light extensively, the removal, or partial removal of these substances by dialysis improved the effectiveness of irradiation. Consequently, when infected allantoic fluid was dialyzed at 4° C. against buffered saline solution of pH 7 for 24 to 48 hours and subsequently exposed to irradiation, it was found that periods of exposure necessary to obtain marked interference with non-dialyzed fluids were far too long for the dialyzed preparations. Under these circumstances the interfering property was destroyed, and the ability to agglutinate chick red cells was reduced

or lost. Whereas non-dialyzed fluids after 30 minutes or more of irradiation still produced influenzal lesions in mice, in the case of dialyzed fluids no pulmonary involvement was noted after inoculation of material irradiated for only 5 to 10 minutes. In non-dialyzed fluids the interfering property could be demonstrated after irradiation for 30 to 60 minutes, whereas dialyzed preparations interfered only when exposure to ultra-violet light was shorter than 30 minutes. With longer exposure the interference diminished rapidly and the test virus grew out (positive red cell agglutination), while controls injected with saline solution instead of with virus gave negative tests (Table 5). This shows that the interfering property is not dialyzable and experiments in which infected allantoic fluid was dialyzed after irradiation confirmed this point. The interfering property of allantoic fluid dialyzed after irradiation for 30 to 60 minutes was left intact. Experiments pertaining to this point are included in Table 5.

TABLE 5.—EFFECT OF DIALYSIS ON INTERFERING PROPERTY

	First injection						Second injection	
		Dialysis					Hemaggl. titer in allantoic fluid 48 hours following injection of	
Exp.	Strain of virus in allantoic fluid		In relation to irradiation	Ratio	Time of irradiation (min.)	Hemaggl. units per ml.	Infectivity for mice	Saline solution	Active virus
1.	WS	−	..	..	60	1024	000000	<2	<2
		+	Before	40:1	60	<2	000000	<2	320
	Normal	−	..	..	60	<2	000000	..	384
2.	WS:	−	..	..	30	384	22100	<2	<2
					60	384	000000	<2	<2
		+	Before	20:1	10	256	000000	<2	<2
					30	256	000000	<2	64
					60	320	000000	<2	384
		+	Before	80:1	5	256	000000	<2	<2
					10	224	000000	<2	16
					30	192	000000	<2	512
					60	64	000000	<2	512
		+	After	80:1	30	320	0000	<2	<2
					60	384	000000	<2	<2
	Normal	−	..	..	30	<2	000000	..	384
					60	<2	..	..	512
3.	PR-8	−	..	..	60	512	D_8D_941	20	20
		+	After	20:1	60	512	D_7440	96	64
	Normal	−	..	..	60	<2	0000	..	512

It was expected, and it is shown in Table 5, that the ratio of volumes between dialyzing fluid and virus preparation was of importance. The more complete the dialysis, the shorter the period of irradiation in which marked interference may be obtained. If the ratio of buffered saline solution to allantoic fluid was 20:1, irradiation for 10 minutes still gave preparations preventing the formation of measurable amounts of hemagglutinin, while with a ratio of 80:1 this was no longer the case. Therefore, in order to have a sufficiently wide range for operation, all fluids for interference experiments were dialyzed against 20 parts of buffered saline solution.

When allantoic fluids were dialyzed in this manner and exposed to ultra-violet irradiation for periods ranging from 1 to 60 minutes, the useful period of exposure, as far as inhibition of hemagglutinin formation was concerned, was found to lie between 1 and 10 minutes, on occasion up to 20 minutes. Table 6 represents a summary of some of the results. Virus irradiated for as little as 1 minute and up to 20

minutes may cause marked inhibition of hemagglutinin formation when injected 3 hours prior to an active test virus, which in control eggs produced high titers. The results appear to be more clear-cut with the WS strain, as no measurable agglutination was found under these conditions, and all fluids from control eggs injected with the irradiated material and saline solution were negative. The PR–8 strain behaved differently, in that low agglutinin titers were found both in control eggs secondarily injected with saline solution and in experimental groups injected with test virus. The titers were below 1:10 in Experiments 5 to 7, when 0.5 ml. amounts of irradiated virus were injected, while higher titers were noted in Experiment 8, in which 1 ml. was given. Only Experiment 4 revealed negative allantoic fluids in both groups when an irradiated fluid of low original red cell agglutinative titer (24-hour-harvest) was used, or when the irradiated virus was diluted nine-fold (Experiment 8*b*). These observations suggested strongly that some hemagglutinin was left free in the allantoic cavity from the injection of irradiated virus, which was not absorbed and could be recovered on harvest 48 hours after the secondary injection of either test virus or saline solution. More evidence for this point will be presented in the subsequent paper.[12]

TABLE 6.—RESULTS OF INTERFERENCE AFTER VARYING TIMES OF IRRADIATION OF DIALYZED INFECTED ALLANTOIC FLUID

	First injection		Second injection 3 hours later	Hemaggl. titer 48 hours following 2nd injection							
				Length of irradiation of 1st inoculum (min.)							
Exp. No.	Strain of virus	Original hemaggl. titer		0	1	3	5	10	20	30	60
1.	WS	384	Saline	112	..	..	<2	<2	..	<2	<2
			Virus	..	..	..	<2	<2	..	64	384
	Normal	<2	Virus	..	..	..	384				
2.	WS	384	Saline	80	..	..	<2	<2	..	<2	<2
			Virus	..	..	..	<2	16	..	352	512
	Normal	<2	Virus	..	..	..	384				
3.	WS	512	Saline	32	..	<2	<2	<2	<2		
			Virus	..	..	80*	<2	40	384		
	Normal	<2	Virus	..	..	..	..	..	512		
4.	PR–8	160	Saline	256	<2	<2	<2	<2	64		
			Virus	..	<2	<2	<2	<2	144		
	Normal	<2	Virus	..	..	..	448				
5.	PR–8	470	Saline	512	7	4	<2	4	24		
			Virus	..	3	2	3	4	80		
	Normal	<2	Virus	..	..	..	448				
6.	PR–8	490	Saline	600	..2	<2	<2	6	<2		
			Virus	..	..3	3	4	<2	96		
	Normal	<2	Virus	..	..	..	448				
7.	PR–8	256	Saline	200	..	3	3	5	2	12	
			Virus	..	..	5	5	4	4	192	
	Normal	<2	Virus	..	..	..	352				
8.	PR–8	512	Saline	..	..	32	16	32	48		
			Virus	..	..	48	64	64	32		
	Same	..	Saline	..	..	<2	<2	<2	32		
	1:9	..	Virus	..	..	<2	<2	<2	28		
	Normal	<2	Virus	..	..	..	1024				

* Two out of 10 allantoic fluids positive.

Another fact should be pointed out here. Experiments 4, 5, and 8*b* in Table 6 show that allantoic fluids from control eggs inoculated with saline solution following the administration of virus irradiated for 1 to 10 minutes were negative in the agglutinative test. When the fluids were irradiated for 20 minutes some virus apparently grew out, since

some hemagglutinins were found, and this could be confirmed by infection of mice. In other experiments the presence of active virus in the irradiated material could be demonstrated only by certain procedures to be outlined in paper II of the series and finally in a number of instances no virus was found but the interfering property was largely intact. In any event, the amount of active virus was so small that the technique of inactivation by ultra-violet irradiation following dialysis was adopted for the present for the study of the interference phenomenon until safer methods for the complete inactivation of virus have been devised which will leave most of the interfering property intact.

Discussion. The observations reported indicated that inactive virus accumulated in the allantoic cavity of the chick embryo infected with influenza A or B, in addition to the active agent. Depending on the relative concentration of the inactive virus, it caused difficulties in passing certain strains of influenza virus by interfering with its propagation. This was notably the case with the Lee strain of influenza B. If one obtained insufficient growth in the subculture (low hemagglutinin titer) it would have appeared correct to use a more concentrated inoculum for subsequent passages, while from the above data the opposite course appears more likely to lead to the desired effect.

The data indicate that correlation between the content of active virus in allantoic fluid and the hemagglutinin titer may exist possibly only during the stage of rapid increase of the active virus, but not after the active virus titer has reached its peak and started to decrease. It is not known, however, whether this process of inactivation is concomitant with the propagation of the active agent.

The amount of inactive virus may be increased in a given preparation by heating to 56° C. or by ultra-violet irradiation, and the inhibition may go as far as to prevent formation of measurable amounts of hemagglutinin. Addition of fresh virus to the irradiated fluids does not overcome the inhibitory effect and it becomes at once apparent that this interference by inactive virus may offer a new means of protection of susceptible cells against infection by the viruses of influenza. Not only for this reason is it worth while to study the phenomenon further, but it may offer, in addition, insight into the mechanism of infection by these agents. The use of the chick embryo for these studies is of added advantage in view of their lacking immunologic response to infection with influenza virus.[4]

Summary. In passing allantoic fluid infected with the virus of influenza A or B to chick embryos by the allantoic route, it was found that concentrated inocula frequently produced less virus than more dilute ones. This inhibition was found to be due to an accumulation of inactive virus in the allantoic fluid interfering with the propagation of the active agent on subculture. Correspondingly, artificial inactivation of the virus by heating to 56° C. or ultra-violet irradiation for short periods of time increased this inhibitory effect.

In order to study this phenomenon more accurately, attempts were made to obtain, on the one hand, non-infectious virus with the interfering property largely intact; and to test, on the other hand, the inter-

ference by the inactive virus with a known amount of the active agent. Ultra-violet irradiation of dialyzed allantoic fluid gave interfering preparations which frequently fulfilled the stated requirements. Primary injection of such irradiated virus into the allantoic sac of the chick embryos, followed by inoculation of active virus within periods of up to 24 hours, prevented the propagation of the active agent.

REFERENCES

1. Anderson, K.: Am. J. Path., **18**, 577, 1942.
2. Andrewes, C. H.: J. Path. and Bact., **50**, 227, 1940.
3. Andrewes, C. H.: Brit. J. Exp. Path., **23**, 214, 1942.
4. Burnet, F. M.: Australian J. Exp. Biol. and Med. Sci., **19**, 291, 1941.
5. Dalldorf, G., and Douglass, M.: Proc. Soc. Exp. Biol. and Med., **39**, 294 1938; J. Immunol., **37**, 245, 1939.
6. Delbrück, M., and Luria, S. E.: Arch. Biochem., **1**, 111, 1942.
7. Doerr, R., and Seidenberg, S.: Ztschr. f. Hyg. u. Infektionskrankh., **119**, 135, 1937.
8. Findlay, G. M., and MacCallum, F. O.: J. Path. and Bact., **44**, 405, 1937.
9. Gildemeister, E., and Herzberg, K.: Deutsch. med. Wchnschr., **51**, 1647, 1925; **53**, 138, 1927.
10. Henle, W., and Chambers, L. A.: Proc. Soc. Exp. Biol. and Med., **46**, 713, 1941.
11. Henle, W., and Henle, G.: Science, **98**, 87, 1943.
12. Henle, W., and Henle, G.: Am. J. Med. Sci., **207**, 717, 1944.
13. Hirst, G. K.: J. Exp. Med., **75**, 49, 1942.
14. Hoskins, M.: Am. J. Trop. Med., **15**, 675, 1935.
15. Jungeblut, C. W., and Sanders, M.: J. Exp. Med., **72**, 407, 1940; **75**, 631, 1942; **76**, 127, 1942.
16. Kunkel, L. O.: Phytopathol., **24**, 437, 1934.
17. Luria, S. E., and Delbrück, M.: Arch. Biochem., **1**, 207, 1942.
18. McKinney, H. H.: J. Agric. Res., **39**, 557, 1929.
19. Magrassi, F.: Ztschr. f. Hyg. u. Infektionskrankh., **117**, 501, 1935.
20. Miller, G. L.: J. Exp. Med., **79**, 173, 1944.
21. Schlesinger, R. W., Olitsky, P. K., and Morgan, I. M.: Proc. Soc. Exp. Biol. and Med., **54**, 272, 1943.
22. Syverton, J. T., and Berry, G. P.: J. Bact., **32**, 356, 1936; Science, **86**, 411, 1937; Am. J. Path., **14**, 633, 1938.
23. Taylor, H. M., and Sprunt, D. H.: J. Exp. Med., **78**, 91, 1943.
24. Thung, T. H.: Cited by Kunkel.[16]
25. White, P. B.: J. Path. and Bact., **44**, 276, 1937.
26. Enders, J. F., and Pearson, H. E.: Proc. Soc. Exp. Biol. and Med., **48**, 143, 1941.

INTERFERENCE BETWEEN INACTIVE AND ACTIVE VIRUSES OF INFLUENZA*

II. Factors Influencing the Phenomenon

By Werner Henle, M.D.

and

Gertrude Henle, M.D.

Philadelphia, Pa.

(From the Department of Pediatrics, School of Medicine, Univ. of Pennsylvania, and the Children's Hospital of Philadelphia)

In the preceding paper it has been shown that influenza virus inactivated under various conditions may interfere with the propagation of the active agent in the allantoic cavity of the chick embryo.[2] This

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Children's Hospital of Philadelphia.

type of interfering phenomenon deserved further attention in view of the fact that it induced rapid protection of susceptible cells. As has been shown, the results of interference did not differ markedly, regardless of whether the irradiated virus was injected 24 hours previous to, or simultaneously with the active test virus. In the present paper, various aspects and factors influencing the phenomenon are analyzed, particularly in regard to prevention of formation of measurable amounts of hemagglutinins following the inoculation of active virus. Problems encountered in the inactivation of virus by irradiation and evidence of the survival of test virus in the allantoic cavity for periods of 24 to 72 hours are presented.

Methods and Materials. The methods used for the propagation of the influenza viruses in the allantoic sac, the techniques employed for the determination of infectivity for mice and chick embryos, and for the assay of hemagglutinins have been described in the preceding paper, as well as the apparatus for ultra-violet irradiation.[2]

Interference Test. Infected allantoic fluids harvested under conditions minimizing bacterial contamination were dialyzed at 4° C. against 20 parts of buffered saline solution of pH 7 for 40 to 48 hours with repeated stirring of the dialyzing fluid. The dialyzed preparations were stored in suitable volumes in the frozen state at −10° to −15° C. for periods of several months without apparent loss of interfering properties. After thawing, the fluids were left at room temperature for at least 30 minutes and centrifuged at 2000 r.p.m. for 30 minutes to remove precipitated matter. The sediment removed was relatively small since the fluids had been dialyzed. Between 15 and 18 ml. amounts of the allantoic fluids were irradiated in open Petri dishes, usually for 3 to 5 minutes, at a distance of 7 inches from a General Electric germicidal lamp (275 μ W/cm^2) under continuous mechanical shaking. The irradiated and bacteriologically sterile fluids may be kept in the refrigerator for several weeks without loss of the interfering quality. For the experiments recorded in this paper, however, the fluids were thawed and inactivated freshly for each test.

Normal allantoic fluid was collected and treated in the same manner. In earlier tests, normal allantoic fluid was used which had been harvested from batches of eggs comparable to those from which the interfering fluids were prepared and after the same total period of incubation. This precaution, however, was found to be unnecessary since the age of the embryo from which the normal allantoic fluid was obtained did not affect the results of the propagation of the test virus. Accordingly, any normal allantoic fluid may be used for the control injection.

For the test, 1 ml. of the irradiated infected or normal allantoic fluid was injected by the allantoic route, followed 14 to 18 hours later by 0.2 ml. of suitably diluted active virus or of saline solution. This increase in interval between the two injections, in contrast to the maximum of 3 hours in earlier experiments, reduced the incidence of non-specific death of embryos. After further incubation of the eggs at 36° to 37° C. for usually 48 hours, the allantoic fluids were harvested individually, and equal amounts of the corresponding liquids pooled. The undiluted individual allantoic fluids were usually tested qualitatively for the presence or absence of hemagglutinins. The pools were titrated for hemagglutinins and infectivity by methods previously described.[2] Individual fluids were similarly assayed when indicated.

Under the conditions described, results of interference experiments were repeatable either when the same starting material was used or when allantoic fluids harvested from eggs under apparently identical conditions were employed.

Experimental. *Quantitative Determination of Interfering Property.* In order to determine the relative amount of interfering agent in the

allantoic fluid, embryos were injected by the allantoic route with various dilutions of irradiated virus and injected 18 hours later either with active virus or saline solution. A control group of eggs injected with normal allantoic fluid followed by active virus served as indicator of the degree of inhibition. As can be seen in Table 1, irradiated PR–8 virus fluids diluted 9 to 81-fold were able to prevent the formation of measurable quantities of hemagglutinin by the test injection of virus. When undiluted or three-fold diluted irradiated virus was injected, hemagglutinins introduced with this injection could be demonstrated when the allantoic fluids were harvested 48 hours after the test injection of virus or saline solution. Dilutions of the irradiated PR–8 virus higher than 1:81 did not prevent the propagation of the test virus as seen by the formation of measurable amounts of hemagglutinins, but even in the case of dilutions of 1:243 or 1:729, the hemagglutinin titer frequently did not equal that of the control allantoic fluids collected from eggs first injected with normal fluid and later with active virus. The activity of the irradiated WS virus preparations usually was weaker, and little or no residual hemagglutinins from the first injection were found at the termination of the tests, while the results with the Lee strain of influenza B were comparable to those obtained with PR–8 virus. Experiment 5 of Table 1 shows an exception to the other experiments recorded in this series, discussion of which will be postponed until a later section of this paper.

TABLE 1.—TITRATION OF INTERFERING PROPERTY

Exp. No.	First injection irradiated virus: Strain of virus	First injection irradiated virus: Infectivity for mice	Second injection 18 hrs. later	Hemagglutinin titer 48 hours after second inoculation following injection of: Irradiated virus in dilution: Und.	1:3	1:9	1:27	1:81	1:243	1:729	Normal allantoic fluid und.
1.	WS (72 hr.)*	0000	Saline	4	<2	<2	<2	<2	<2	<2	
			Virus	8	64	512	768	768	512		512
2.	WS (96 hr.)	00000	Saline	<2							
			Virus	<2	112	320	512	..	..	..	640
3.	PR–8 (72 hr.)	0000	Saline	32	3	<2	<2	<2	<2	<2	
			Virus	48	8	<2	<2	<2	3	320	768
4.	PR–8 (72 hr.)	000	Saline	16	6	<2	<2	<2	<2	<2	
			Virus	64	3	<2	<2	<2	128	1024	1024
5.	PR–8 (24 hr.)	..	Saline	14	<2	<2	<2	40	64		
			Virus	7	<2	<2	<2	32	448	..	512
6.	PR–8 (48 hr.)	..	Saline	28	..	<2	<2	<2	<2		
			Virus	12	..	<2	<2	4	128	..	512
7.	PR–8 (96 hr.)	..	Saline	24	4	<2	<2	<2	<2	<2	
			Virus	16	3	<2	<2	<2	70	256	512
8.	PR–8 (72 hr.)	00000	Saline	48	3	<2	<2	<2	<2		
			Virus	32	8	<2	<2	256	512	..	1024
9.	Lee (72 hr.)	0000	Saline	24	3	<2	<2	<2	<2		
			Virus	16	4	<2	<2	64	384	..	1024
10.	Lee (72 hr.)	0000	Saline	..	..	<2	<2	<2	<2		
			Virus	..	..	<2	<2	4	192	..	768

* (72 hr.) = the incubationary period of virus used for irradiation.

It was considered that the concentration of active virus in the test dose used for demonstrating the interfering property of a given irradiated fluid might conceivably influence the results. Table 2 shows an

experiment concerning this point. There was no apparent difference in the degree of interference, whether 3,000,000 or 30 50%-infectious doses (ID_{50}) were injected into the allantoic sac primarily inoculated with inactivated virus. The allantoic fluids of all embryos first injected with irradiated PR–8 virus diluted 1:3 showed some residual hemagglutinins from this injection as shown by the controls tested with saline solution instead of virus. When the interfering fluid was diluted 1:9 to 1:81, formation of measurable amounts of hemagglutinin was prevented, irrespective of the concentration of test virus. When the irradiated preparation was diluted 1:243, test virus grew out in all eggs, although with the more dilute inocula of test virus (30 to 300 ID_{50}) the resulting hemagglutinin titer was lower than following administration of the more concentrated active virus. This and similar experiments indicated that the interference by inactive virus cannot be overcome by excessive amounts of test virus. In the limiting dilutions of interfering fluid, a small dose of active test virus may require longer incubation until all the remaining fully susceptible cells are infected, whereas larger doses of active virus may require only a short period. Prolongation of the incubationary period, therefore, would probably have eliminated this difference between the hemagglutinin titers following larger doses of test virus and those resulting from smaller doses.

TABLE 2.—INTERFERENCE IN RELATION TO CONCENTRATION OF TEST VIRUS

Number of ID_{50} in test virus injection	Hemagglutinin titer 48 hours after test inoculation following injection of: Irradiated virus in dilution 1:3	1:9	1:27	1:81	1:243	Normal allantoic fluid und.
3×10^5	7	<2	<2	<2	128	384
3×10^4	4	<2	<2	<2	256	384
3×10^3	7	<2	<2	<2	128	288
3×10^2	3	<2	<2	<2	112	320
3×10^1	8	<2	<2	<2	48	288
3×10	3	<2	<2	2	40	512
Saline	3	<2	<2	<2	<2	

Influence on Interference of Incubationary Period of Virus Used for Irradiation. In earlier experiments the impression was gained that the interfering property of irradiated virus was particularly pronounced in allantoic fluids harvested after extended periods of incubation, *i. e.*, fluids collected 72 to 96 hours after inoculation, appeared to be more suitable than fluids harvested after 24 to 48 hours. When this was checked with the present technique it could not be verified. Several hundred 10-day-old embryos were inoculated by the allantoic route with a suitable dilution of PR–8 virus and comparable groups of eggs were harvested after 24, 48, 72, and 96 hours of incubation. The respective allantoic fluids were dialyzed together against 20 parts of buffered saline for 40 hours. When these fluids were irradiated for 90 seconds and then compared with each other in interference tests, no great differences could be noted. The results of the agglutination test are shown graphically in Figure 1. All fluids in dilution 1:81 prevented the formation of hemagglutinins following the test virus injection. A dilution of 1:243 and 1:729 gave only limited reductions in titer as compared with the controls. Longer irradiation of the fluids (3 or 5

minutes) destroyed some of the interfering property of fluids harvested after 24 hours and 48 hours, but the results of the 72- and 96-hour fluids were not markedly different from the results obtained after irradiation for 90 seconds. Longer periods of irradiation, as shown previously,[2] may destroy the interfering property also in these fluids. The relative constancy of interference by the various fluids were somewhat unexpected, in view of the differences in their hemagglutinin titer. It was only one-third as high in the 24-hour fluid as in the 48- and 72-hour preparations, while the 96-hour material was lower again probably because of the removal of larger amounts of precipitated matter following freezing and thawing. The hemagglutinin titers were, in order of the collection of the fluids, 1:160; 1:470; 1:490; and 1:356. Determinations of the infectivity of the allantoic fluid immediately after harvest showed that the fluids contained $10^{6.3}$ $10^{6.5}$ $10^{6.1}$ and $10^{5.3}$ 50%-mortality doses for mice per milliliter.

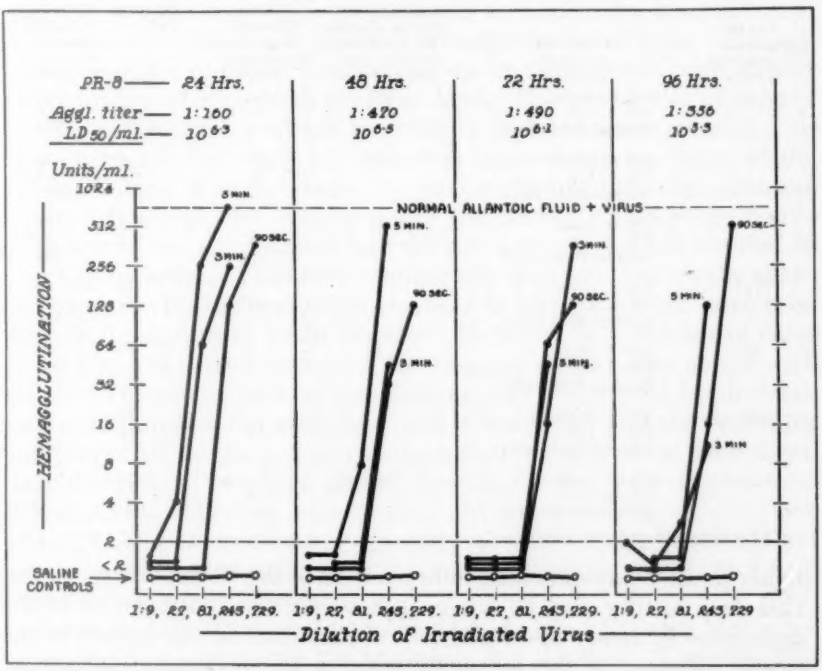


FIG. 1.—Relation between the incubation period of virus used for irradiation and the degree of interference.

Length of Period of Protection. In the experiments reported thus far, the interfering property was usually tested with active virus 14 to 18 hours after the primary inoculation of the irradiated material. In a few tests the active virus was given simultaneously with or immediately after the irradiated fluid, in others as late as 24 hours afterwards. The following experiment extends this range from 96 hours before to 24 hours after the inoculation of the test virus. Several hundred 8-day-old

embryos were received, and groups of them inoculated in the allantoic sac with undiluted or nine-fold diluted irradiated allantoic fluid infected with the PR–8 strain or with normal fluid, either on the same day or one of the three following days. On the 12th day of embryonic development one-half of the eggs in each group were injected with active virus and the other half with saline solution. In addition, a number of untreated 12-day-old embryos were inoculated with test virus to receive the interfering material 3 or 24 hours after the active agent. As shown in Table 3, all eggs inoculated with undiluted interfering fluid showed residual agglutination of red cells because of this injection. The titer in all these preparations did not differ markedly, in spite of the fact that the titer in the allantoic fluids harvested from other eggs immediately after the primary injection was about four-fold

TABLE 3.—LENGTH OF PERIOD OF INTERFERENCE

First injection			Second injection		
Age of embryo at 1st injection in days	Irradiated material injected	Hemagglutinin titer in allantoic fluid immediately after 1st injection	Time between 1st and 2nd injection in hours	Hemagglutinin titer 48 hours following injection of	
				Saline	Virus
8	PR–8, undil.	122	..	12	16
	PR–8, 1:9	..	96	<2	<2
	Normal fluid undil.	..	..	..	384
9	PR–8, undil.	90	..	4	12
	PR–8, 1:9	..	72	<2	3
	Normal fluid undil.	..	..	..	256
10	PR–8, undil.	77	..	8	16
	PR–8, 1:9	..	48	<2	16*
	Normal fluid undil.	..	..	..	384
11	PR–8, undil.	..	..	32	16
	PR–8, 1:9	..	24	<2	<2
	Normal fluid undil.	..	..	..	384
12	PR–8, undil.	50	..	16	24
	PR–8, 1:9	..	0	<2	<2
	Normal fluid undil.	..	..	..	256
12	PR–8, undil.	..	..	32	16
	PR–8, 1:9	..	−3	<2	16
	Normal fluid undil.	..	..	..	384
13	PR–8, undil.	30	..	24	512
	PR–8, 1:9	..	−24	<2	512
	Normal fluid undil.	..	..	..	512

* Four out of 10 embryos infected.

higher in the 8-day-old chick embryos than in the 13-day-old specimen. This drop in titer may be due in part to additional absorption of the agglutinins by newly developed cells of the allantoic sac, in part to the greater dilution of the hemagglutinins in the increasing volume of allantoic fluid during this stage of embryonic development, and finally, perhaps to a slight extent to destruction of hemagglutinins at 37° C., although test tube experiments did not reveal any loss of titer during incubation periods of similar length. As far as the interfering property was concerned, allantoic fluids from eggs receiving the irradiated virus as early as 96 hours before inoculation of the test virus did not show measurable amounts of hemagglutinin in the groups injected with nine-fold diluted interfering fluid, and no increase in titer in those prepared with the undiluted material. When the irradiated virus was injected 3 hours after the test virus, marked

reduction of hemagglutinin formation could still be obtained, while after 24 hours no effect was noted.

Removal of Free Irradiated Virus From the Allantoic Cavity. In the experiments thus far recorded, irradiated virus was injected into the allantoic cavity and frequently residual hemagglutinin could be demonstrated in the allantoic fluid of such eggs when harvested after various intervals of incubation. It was conceivable that the presence of this free irradiated virus in the allantoic fluid was responsible for the interference, and removal of it was considered essential. This was accomplished in a few experiments with slightly older embryos, *i. e.*, at the 12th day of incubation. Two holes were drilled just through the shell without injuring the shell membrane or underlying tissues. One of these was placed on one side from the embryo over the lower third of the allantoic sac, the other on the opposite side, 2 to 3 mm. under the air sac. Rubber disks of 4 to 5 mm. diameter and about 2 mm. thickness were pasted onto the shell over the holes with a heavy solution of collodion which was allowed to harden for several hours. The irradiated virus was injected through the lower hole. The egg was placed in an upright position and an 18-gauge needle with a short bevel was inserted through the same hole. This needle was connected by fine rubber tubing with a reservoir of buffered saline solution. In some instances the irradiated virus was injected into the lumen of the rubber tubing directly above the needle leading into the allantoic cavity. Through the opening under the air sac, an 18-gauge needle with one or two holes drilled into the side near the tip was inserted to serve as an outlet. The saline solution was then run through the allantoic cavity. By this technique amounts as high as 200 ml. have been flushed through in 15 to 20 minutes. However, in a number of cases much less was passed because of the clogging of the outlet needle with tissue. The effectiveness of this flushing was ascertained by determination of urates in the wash fluid, and it was found that the first three samples of 10 ml. each removed more than 93% of these substances, and after 60 ml. had been passed through the sac, only a fraction of 1% was left. This test actually may not reflect the true effectiveness of the flushing of the allantoic sac, since precipitates of urates are found on the membrane of embryos of this age and the removal of these may cause considerable difficulties.

After the allantoic sac had been flushed, the eggs were incubated again for 24 hours before the test virus was injected. The results of some of these tests are shown in Table 4. Only results from embryos flushed with 100 ml. of buffered saline solution or more are included. This amount was passed within 12 to 40 minutes. As seen in the table, eggs receiving only the injection of irradiated virus show a residual hemagglutinin titer in the allantoic fluid when harvested 72 hours later (eggs numbers 1 to 4). Eggs injected with irradiated virus, flushed thereafter with saline solution, and tested with virus 24 hours later did not contain measurable amounts of hemagglutinin within the allantoic sac when its contents were collected 48 hours after the inoculation of the test virus. This was the case when the flushing was begun

before or immediately following injection of the irradiated virus into the lumen of the rubber tubing (eggs numbers 5 to 8) or when flushing was started 30 to 60 minutes after the first injection (eggs numbers 9 to 14). Allantoic fluids of eggs not injected with irradiated virus but flushed with buffered saline solution and inoculated with active virus showed the usual high titer in the hemagglutinin test (eggs numbers 15 to 18) as did those from eggs injected only with the test virus (pool of eggs 19 to 25). The mortality of the embryos undergoing this procedure is fairly high but it is hoped to improve the technique for more extended studies of the phenomena involved in interference. Thus far only embryos of 12 days' incubation at the start of the experiment have been used, since there was too high a loss of younger embryos as a result of the procedures. Consequently, periods of protection of longer than 24 hours have not been tested yet.

TABLE 4.—REMOVAL OF RESIDUAL IRRADIATED VIRUS FROM THE ALLANTOIC CAVITY

		Flushing of allantoic sac			Second injection 24 hours after 1st	
Egg No.	First injection irradiated virus (ml.)		After 1st injection (min.)	Flushed through (ml.)	Test material	Hemagglutinin titer 48 hours after 2nd injection
1	1	−	−	−	Saline	12
2	1	−	−	−	Saline	16
3	1	−	−	−	Saline	16
4	1	−	−	−	Saline	16
5	1	+	0*	132	Virus	<2
6	1	+	1†	119	Virus	<2
7	1	+	1	110	Virus	<2
8	1	+	1	118	Virus	<2
9	1	+	30	115	Virus	<2
10	1	+	30	120	Virus	<2
11	1	+	60	102	Virus	<2
12	1	+	60	110	Virus	<2
13	1	+	60	102	Virus	<2
14	1	+	60	160	Virus	<2
15	0	+	−	102	Virus	256
16	0	+	−	135	Virus	192
17	0	+	−	160	Virus	512
18	0	+	−	108	Virus	288
19-25 pool	0	−	−	−	Virus	320

* Irradiated virus injected into rubber tubing while flushing at a rate of 10 ml. per min.
† Irradiated virus injected into rubber tubing and flushing started immediately thereafter.

Interference as Measured by Titration of Active Virus. In the preceding pages various aspects of the interference of inactivated virus with the propagation of the active agent have been discussed in regard to the development of agglutinins for chick red cells. Absence of measurable hemagglutinin formation can be taken as an index of marked reduction in propagation of virus, but it is not an absolute measure. In the technique used in this laboratory, the agglutinin test becomes positive only after the infectivity has already reached a fairly high titer, *i. e.*, the infectivity for mice in an allantoic fluid may reach up to 10,000 LD_{50} per ml. before agglutination may be observed. Evidence of this statement is included in the first paper of this series.[2]

It is necessary, therefore, to review the experiments recorded in regard to the propagation of the virus as measured by infectivity. Such an analysis has to consider three possibilities: (*a*) active virus may have been left in the irradiated material which, however, may

have been prevented from adequately multiplying by an excess of inactive virus (interference); (*b*) the test virus injected into the allantoic cavity following the primary injection of irradiated virus, although prevented from infecting susceptible cells by interference, may survive in the allantoic fluid for a certain length of time at 37° C., and some of it may be present at the time of harvest 48 hours later; (*c*) in limiting dilutions of interfering fluid, finally, or after excessive irradiation of it, not all susceptible cells may be blocked by inactive virus, and the test virus may actually propagate. The last point does not require any further comment. The first two, however, were studied more closely. It will be shown that either development is possible and, in fact, both may coëxist in one experiment.

TABLE 5.—DEMONSTRATION OF SURVIVING VIRUS IN IRRADIATED ALLANTOIC FLUID BY PROLONGED EXPOSURE TO ULTRA-VIOLET LIGHT OR BY DILUTION

Inoculum used for subculture (PR–8 virus)		Results obtained with allantoic fluids of subcultures	
Time of irradiation	Dilution of inoculum	Hemagglutinin titer in allantoic fluid	Infectivity for mice
3 min.	Und.	32	00000
	1:3	3	00000
	1:9	<2	2 ± ±0
	1:27	<2	D_3 ±00
	1:81	<2	Und. 3321 10^{-1} 1 ±00
5 min.	Und.	24	000000
10 min.	Und.	24	± ±0000
20 min.	Und.	48	$D_3D_7D_7D_3D_3D_3$

Survival of Active Virus in Irradiated Fluids. Prolonged irradiation or dilution of the irradiated allantoic fluid may reduce the interfering property sufficiently to permit small quantities of surviving active virus to multiply and form measurable amounts of hemagglutinin (Exp. 5, Table 1, and paper 1[2], Table 6). Frequently the virus may not reach the level where agglutination of red cells becomes positive, but its presence may be ascertained by inoculation of either chick embryos or mice. Table 5 summarizes an experiment combining the two ways of demonstrating the presence of some residual active virus in irradiated fluid, namely, prolonged irradiation and dilution. As seen in the table, when infected allantoic fluid irradiated for 3 minutes was inoculated either undiluted or in dilution 1:3 by the allantoic route, some residual hemagglutinins were found on harvest, but not when higher dilutions were injected. When the allantoic fluids of the subcultures were inoculated intranasally into mice, those derived from the more concentrated inocula of irradiated virus did not cause apparent pulmonary lesions, while those from higher dilutions produced typical involvement. When the allantoic fluid was irradiated for 3, 5, 10, or 20 minutes and injected without dilution into eggs, all subcultures showed free hemagglutinins from this injection, but inoculation of mice with the fluids derived from virus irradiated for the shorter periods of time did not result in lung lesions, while those from virus treated for 20 minutes caused death with typical pathology. From this and similar experiments, it is apparent that at least 100 ID_{50} of

active virus may be present in an irradiated fluid, which amount could escape detection if the fluid were injected undiluted only and if one depended on the hemagglutination test alone. In order to judge the degree of inactivation of virus by irradiation, therefore, extensive tests have to be performed.

Survival of Virus Injected as Test Inoculum. It was conceivable that some active virus from the test inoculation may survive long enough in the allantoic fluid to be demonstrable 48 hours later at the termination of an experiment. This assumption was verified in the following manner. Several hundred 10-day-old chick embryos were injected by the allantoic route with either irradiated PR–8 virus diluted 1:9, or with irradiated normal allantoic fluid in the same dilution. After further incubation of the eggs for 14 hours, some of the eggs in each group were tested either with active virus (10,000 or 1,000,000 ID_{50}), or with saline solution. Of each group, 10 eggs were placed at −10° C. immediately after the test inoculation, or after 2, 24, 48, and 72 hours of further incubation at 37° C. The allantoic fluids were collected aseptically after chilling of the eggs for at least 30 minutes and adequate samples of the pooled fluids from each group were stored in sealed ampules at −70° C. until titration for virus activity in eggs could be performed.

The results of this experiment are summarized in Figure 2. In the left part of the figure the hemagglutinin titers have been plotted against the time of incubation while the right side shows the infectivity tests. The hemagglutination reactions gave the usual results. The irradiated virus had been diluted sufficiently to prevent complication of the test by residual hemagglutinins from the primary injection, but it was sufficiently concentrated to interfere with the formation of measurable amounts of hemagglutinin for at least 48 hours of incubation. After 72 hours the stronger test dose (0.5 ml. 10^{-2}) gave slightly positive results in 8 out of 9 allantoic fluids. The allantoic fluids collected from eggs primarily injected with normal allantoic fluids gave the usual high titers in the agglutination test in 24 hours, and further increases were noted up to 48 or 72 hours of incubation.

When the allantoic fluids from eggs inoculated after the injection of interfering fluid with the smaller test dose (0.5 ml. 10^{-4}) were titrated by the allantoic route, it could be shown that all contained active virus regardless of whether they were harvested shortly after the test inoculation or 72 hours later. The highest titers (ID_{50}/ml.) were found in the earliest harvests. With prolonged incubation, the titer decreased gradually until after 72 hours approximately 10% of the original amount could be demonstrated. The allantoic fluids from the groups of eggs inoculated with the larger dose of test virus seemed to follow the same general trend in the first few harvests, but the titer then remained more or less constant. The difference in active virus content between the groups tested with the two dilutions of virus were in the order to be expected, *i. e.*, the allantoic fluid from eggs inoculated with the larger dose contained about 50 to 100 times more virus. Comparison of the fluids from eggs inoculated with the virus dilutions

after a primary injection of normal allantoic fluid showed that the more dilute inoculum gave the better response, in agreement with the findings reported in the preceding paper.[2] There was no significant difference in regard to the "0-hour-harvests" in the two corresponding series. However, in the next two hours a slight decrease in titer occurred in the two control series, signifying greater absorption of the virus as compared with the results in the interference-groups, which showed no such marked fall in active virus concentration. Whether or not this constitutes a significant difference between the experimental and control groups remains to be seen in further studies. Any

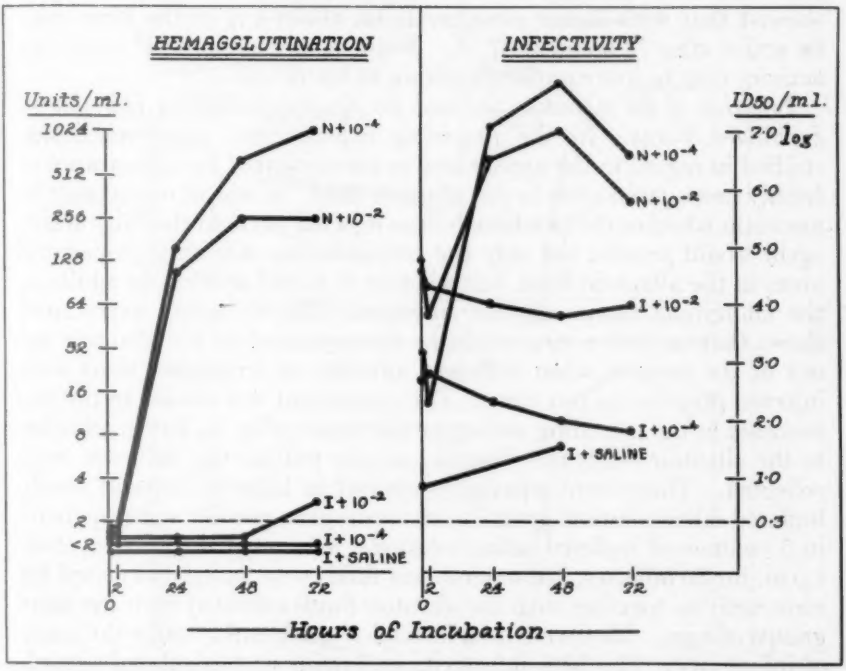


FIG. 2.—Demonstration of survival of active virus from test inoculation in the allantoic fluid for a period of 72 hours. $N + 10^{-2}$, $N + 10^{-4}$—normal allantoic fluid injected prior to test virus diluted 10^{-2} or 10^{-4}; $I + 10^{-2}$, $I + 10^{-4}$—irradiated virus injected prior to test virus diluted 10^{-2} or 10^{-4}.

quantitative assay of absorption of the active virus is hampered by various factors. It is obvious that during the cooling down period of the eggs at $-10°$ C. absorption of the virus may continue. However, this period was kept as closely similar as possible for the early harvests. Although the approximate amount of active virus injected was known, any calculations of how much should be recovered in the allantoic fluid of the injected egg are difficult in view of the fact that the amounts of allantoic fluid per egg during this stage may vary considerably, as also may the size of the allantoic sac and the number of susceptible cells. For this reason the apparent differences shown in Figure 2

should be considered only as preliminary observations until a more extended study has been made.

The experiment recorded shows definitely that virus from the test inoculation may survive in the allantoic sac for the period of time usually accorded to these interference experiments. Tests conducted *in vitro* were found to strengthen this observation. Concentrations of virus similar to those shown in Figure 2 were added to normal allantoic fluid in the approximate amount encountered in the eggs. The mixtures were kept in 3 ml. amounts in individual ampules at 37° C., and one each removed after the indicated time of incubation. The ampules were stored at −70° C. until the titration could be done. The results showed that with higher concentrations, about 1% of the virus may be active after 72 hours at 37° C. With smaller amounts of virus, the activity may be lost completely within 48 hours.

Infection of the Allantoic Sac and the Embryo Following Injection of Irradiated Virus. In the preceding experiments, interference was studied in regard to the appearance or prevention of the appearance of freshly propagated virus in the allantoic fluid. It was of importance to ascertain whether the irradiated virus injected prior to the fully active agent would prevent not only the accumulation of freshly propagated virus in the allantoic fluid, but whether it would protect, in addition, the embryonic tissues against infection. The following experiment shows that no active virus could be demonstrated in the allantoic sac nor in the embryo when sufficient amounts of irradiated virus were injected prior to the test virus. The experiment was similar to the one recorded in the preceding section of this paper (Fig. 2), but in addition to the allantoic fluids the allantoic sacs as well as the embryos were collected. These were repeatedly washed in large volumes of sterile buffered saline solution, ground with sterile glass powder and suspended in 5 volumes of buffered saline solution. After centrifugation at 2000 r.p.m. for 30 minutes, the supernatant fluids were saved and tested for virus activity together with the allantoic fluids collected from the same groups of eggs. Mice were used instead of chick embryos for the assay of infectivity. The 50%-infectivity end-point was calculated according to the method of Reed and Muench instead of the mortality end-point, since in the interference groups little or no mortality occurred. Only mice showing definite lesions were included in the calculations, while doubtful results (±) were disregarded. The results of this experiment are summarized in Figure 3. As seen in the figure, the results of the agglutinative test (upper two charts) showed the usual findings. In the left half, where the interference groups are plotted, residual hemagglutinins from the primary injection of irradiated virus were demonstrable in the allantoic fluids from immediately after the injection until the termination of the experiment, during which period a slight decrease in titer occurred. The test virus injected 18 hours after the first treatment did not increase the hemagglutinin titer. Suspensions of membranes and embryos did not agglutinate red cells. The right half of the figure, which gives the control data, shows a rapid increase of hemagglutinins after the 12th hour of incubation in the allantoic

fluid and to a lesser degree in the suspension of allantoic membranes. The embryos, however, did not react in this test.

The infectivity tests are plotted in the lower two charts of Figure 3. The irradiated virus did not produce demonstrable amounts of active virus in the allantoic fluid nor in the embryo or membranes (saline controls). Test injection of approximately 1000 ID_{50} (for the chick embryo) into the eggs primarily treated with irradiated virus, showed again the survival of some of this test virus for 48 hours in the allantoic

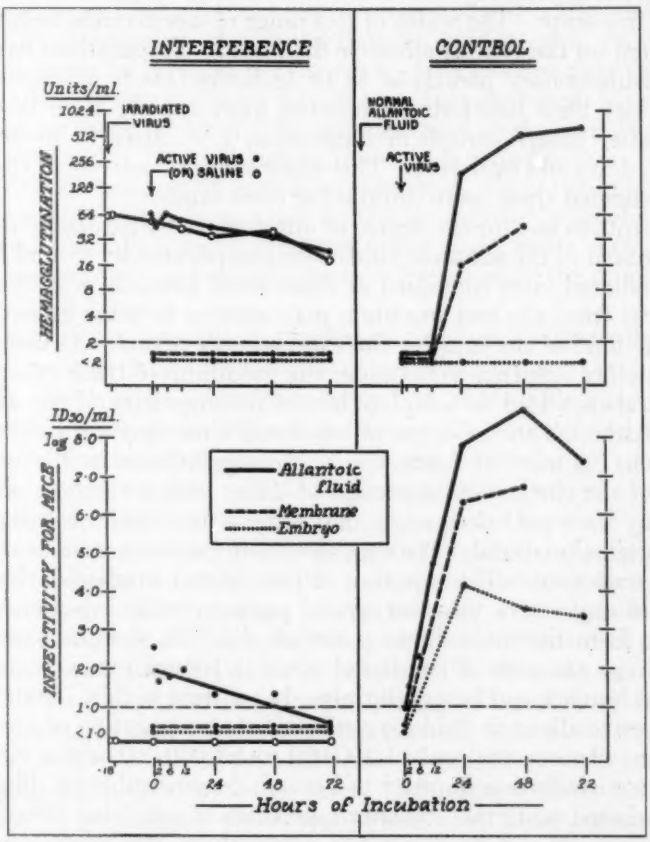


FIG. 3.—Prevention of infection of embryonic tissues by interference.

fluid. No active virus could be demonstrated in the membranes and embryos of these eggs. On the other hand, the controls, prepared by preliminary injection of irradiated normal allantoic fluid, revealed active virus in all three preparations. The highest infectivity titer was found in the allantoic fluid, followed by the membrane suspension and the embryos. This experiment showed, then, that the irradiated virus effectively blocked passage of the active agent into the embryonic tissues and protected them from infection.

Discussion. The interfering property of irradiated influenza virus with the propagation of the active agent was readily demonstrated in the allantoic sac of the chick embryo. This structure was particularly suited to such tests because of its even and relatively small total surface, in contrast to that of the complicated mammalian respiratory tract. Under optimal conditions, approximately 0.01 ml. of the irradiated allantoic fluids containing influenza virus prevented the formation of measurable hemagglutinins. This result depended somewhat on the technique of irradiation. Too intense or too long exposure destroyed the interfering property; too little irradiation left too much virus in the fully active state. The width of this range of interference, in turn, was dependent on the type of allantoic fluid used. Preparations harvested after incubationary periods of 24 or 48 hours (11- to 12-day-old embryos) lost their interfering properties more rapidly than fluids collected after longer periods of incubation, *i. e.*, after 72 to 96 hours (13- to 14-day-old embryos). This wider range of activity of the latter fluids rendered them more suitable for these studies.

Attempts to test for the degree of interference by titrating the active virus present in the allantoic fluids were complicated by several factors. The irradiated virus contained at times small amounts of active virus. and virus from the test inoculum may survive to some extent in the allantoic fluid of the eggs for the experimental period. As mentioned, irradiation of influenza virus under the conditions of these experiments did not always lead to complete loss of pathogenicity of the allantoic fluid. Although the injection of irradiated virus may not produce any symptoms in mice or formation of hemagglutinins in the allantoic cavity of the chick, second passage of either mouse lungs or allantoic fluid may show not infrequently that some active virus was still present in the original material. The experiments in the chick were on occasion quite paradoxical. The injection of less diluted irradiated virus may not yield any active virus on second passage, while injection of subcultures from the more dilute materials did. On the one hand, relatively large amounts of irradiated virus (1/100 ml.) were required to suppress formation of hemagglutinins. In contrast to this, 1/100,000,000 ml. of active allantoic fluid may still initiate propagation of virus, and it became obvious that only 1/100,000 to 1/1,000,000 of the virus had to survive irradiation in order to become demonstrable on dilution of the irradiated material. Smaller quantities of surviving virus (up to 100 ID_{50}) could not be recognized under these conditions, since the inactive virus will interfere with its propagation. Such small amounts of the active agent, or any minute amount of freshly propagated virus did not retain activity at 37° C. for extended periods of incubation, as has been demonstrated by studying the survival of dilute inocula in the allantoic sac previously treated with irradiated virus. Small quantities of test virus may be inactive within 48 hours of incubation at 37° C., while with larger doses a certain percentage may survive for at least 72 hours.

Similar results were obtained on prolonged irradiation of the virus. The interfering property was gradually lost with increased time of

exposure, and was no longer demonstrable at a time when small quantities of active virus were left. It is obvious from these experiments that it is difficult to ascertain complete inactivation of a given preparation of influenza virus, and as long as only the undiluted irradiated 24 culture is tested, no reliable information is gained. These data will have to be considered in employing and evaluating vaccines inactivated by irradiation from the point of immunogenic activity and safety. The superiority of irradiated influenza vaccines as compared with formalinized preparations has been demonstrated,[4] and may be due in part to surviving but not readily demonstrable active virus.

As to the mechanism of this interference phenomenon, no definite explanation can be given at the moment. It is obvious that the inactivated virus is responsible for this effect. This statement is based on the following facts, which will be demonstrated more extensively in a subsequent paper. The interfering property is found only in infected allantoic fluids and not in normal preparations. It is non-dialyzable, is sedimentable in the high-speed centrifuge together with the active agent, and neutralization of irradiated influenza A fluids with specific anti-influenza A serum prevents the interference with the propagation of influenza B virus.

Hemagglutinins present in irradiated infected allantoic fluid are adsorbed to some extent by the cells of the allantoic sac. Attempts to ascertain the rate of adsorption have met with difficulties. Such determinations are dependent on the size of the allantoic sac and the amount of allantoic fluid present in the egg causing dilution of the inoculum; the strain from which the hemagglutinin was derived, and finally possible elution of the hemagglutinin from the cells.[3] In spite of these handicaps, a few results appear quite definite. Elution of the virus after adsorption could not be ascertained from consideration of the flushing experiments. Eggs inoculated with irradiated virus and flushed with buffered saline solution immediately afterwards, did not reveal any hemagglutinins in the contents of the allantoic sac 48 or 72 hours later. Unless elution occurred during the period of flushing, enough hemagglutinin could have been released to produce a positive test in these harvests. After adsorption of irradiated virus, no additional adsorption of virus takes place. Altogether, these statements are based on preliminary observations, and with improvement of the techniques employed, their validity has to be tested.

The flushing experiments have shown that the susceptible host cell may be changed very rapidly and the tissues may become refractory to infection with the influenza virus for at least 24 hours following contact with the irradiated agent. Since the test virus usually survives for more than 24 hours in the allantoic sac, the period of protection measured actually more than 48 hours. The change in susceptibility prevents the passage of the virus from the lumen of the allantoic sac into the membrane and embryonic tissues, but infection of the embryo by routes other than the allantoic does not inhibit the growth of the virus, as will be shown in a later publication.

Summary. Study of various aspects of interference between inactive influenza virus and the propagation of the active agent has given the following results:

1. Injection of approximately 0.01 to 0.005 ml. of irradiated virus (allantoic fluid) into the allantoic cavity will suppress formation of measurable amounts of hemagglutinin from a subsequent inoculation of active test virus.

2. The concentration of test virus has no influence on the results. They are similar regardless of whether 10 or 10 million ID_{50} are injected for testing.

3. No striking differences in interfering property were noted between irradiated allantoic fluids derived from virus cultures incubated for 24, 48, 72, or 96 hours. However, the interfering property in the earlier harvests (younger embryos) was more susceptible to destruction by ultra-violet light.

4. The interfering injection could be given as early as 96 hours before the test virus and up to 3 hours afterwards and produce extensive interference. When injected 24 hours after the active virus, no protection was noted.

5. Flushing of the allantoic sac with more than 100 ml. of saline solution following the injection of irradiated virus to remove free hemagglutinins, did not eliminate the interference. The protection of susceptible cells occurs very rapidly, since injection of the irradiated virus into the egg during flushing also prevented active virus from multiplying when injected 24 hours later.

6. Active virus frequently found in the allantoic fluid of the experimental eggs may be derived from 3 sources: (*a*) small amounts of virus may survive irradiation and enter with the first injection; (*b*) virus from the test inoculation may retain activity to some extent at 37° C. for the experimental period; (*c*) virus may actually propagate when limiting dilutions of irradiated virus were used for the primary injection.

7. Survival of active virus in irradiated preparations sometimes may be demonstrated only after dilution or prolonged irradiation of the allantoic fluid. Both steps decrease the interfering property and permit small quantities of surviving active virus to propagate.

8. The interfering injection prevents the test virus from entering and propagating in the embryonic tissues.

While these manuscripts were in press, an article by Ziegler, Lavin and Horsfall appeared,[5] which confirmed our observations previously reported.[1] These authors differentiate between partially inactivated and non-infective preparations of irradiated virus. This differentiation appears somewhat arbitrary in view of the fact that complete inactivation of influenza virus cannot be ascertained in the presence of the interfering agent. As a matter of fact, Ziegler and his co-workers come to the same conclusion when discussing their results.

The findings reported by these workers are generally in good agreement with our results, with the exception that we failed to note differences in interfering properties of influenza A and B virus. The differences between the PR-8 and Lee strains recorded by Ziegler *et al.* might well be incidental findings, and other preparations of these strains might have given different results. One also has to consider that a certain amount of additional inactive virus may be introduced with larger doses of the active test virus (cp. Ref. 2), a phenomenon particularly noticeable with the Lee strain of influenza B

virus. Such small amounts of additional inactive virus could well be responsible for small apparent differences in interferring properties where no quantitative methods of hemagglutination are employed.

REFERENCES

1. HENLE, W., and HENLE, G.: Science, **98**, 87, 1943.
2. HENLE, W., and HENLE, G.: AM. J. MED. SCI., **207**, 705, 1944.
3. HIRST, G. K.: J. Exp. Med., **76**, 195, 1942; **78**, 99, 1943.
4. SALK, J. E., LEVIN, J. I., and FRANCIS, T., JR.: J. Exp. Med., **72**, 729, 1940.
5. ZIEGLER, J. E., LEVIN, G. I., and HORSFALL, F. L., JR.: J. Exp. Med., **79**, 379, 1944.

ONE YEAR OBSERVATIONS OF THE TREATMENT OF CANCER WITH AVIDIN (EGG WHITE)

BY IRA I. KAPLAN, B.S., M.D.

DIRECTOR, RADIATION THERAPY DEPARTMENT, BELLEVUE HOSPITAL; CLINICAL PROFESSOR OF SURGERY, NEW YORK UNIV. COLL. OF MEDICINE
NEW YORK, N. Y.

WHEN our preliminary report[10] on avidin was presented about 1 year ago, it received some entirely undesired and regrettable newspaper publicity. As the authors stated at the time, the whole matter was still in the experimental stage and the procedure was not to be regarded as a cure. Unfortunately the lay public can rarely be made to understand that such experimentation must be carried on for a long period of time before any definite claims may properly be advanced, and thus it is that the simple announcement of any new procedure at once arouses unfounded hopes for a cure having been discovered.

Now that more than a year has elapsed since the experimental work with avidin was initiated, a year during which it was carefully and scientifically carried on, we feel warranted in making a further report so that both the profession and the laity may be informed of the results of our experimental investigation and an evaluation made of the proposed method of treatment.

In June 1942, following the reports of many workers[2,3,8,11,19,20] on the potent influence of biotin on cellular growth and the observations of others that egg white,[1,6,13,14] or more precisely, its constituent, avidin, possesses the ability to deprive the human system of biotin[16] and thus, as Laurence suggested,[12] possibly inhibit the influence of biotin on abnormal cell growth, it occurred to us to carry out some preliminary clinical trials as tests[4,5,7,9] of the hypothesis that malignant cells required biotin for their metabolic functions, and that egg white might seriously interfere with the vital function of malignant cells and thus bring about their destruction.

It was our thought to evaluate clinically this theory of control of carcinogenesis through diet, merely by substituting sufficient quantities of egg white in the diet of selected groups of patients, in place of a quantity of biotin-containing foods.

Procedure. As there was as yet no definite quantitative standard for measuring the amount of avidin required to neutralize biotin in the human system, the amount of egg white employed in these clinical experiments was necessarily chosen empirically, using Sydenstricker's[18] formula as a pattern.

For this experimental study,* 10 cases were chosen, with definite specific malignant lesions, which could readily be visually and clinically identified, and the changes, if any, readily recognized. In 3 cases, avidin therapy alone was used; in the others, Roentgen ray therapy was employed in addition to the egg white treatment, in order to determine whether or not avidin increased the tumor radio responsiveness to Roentgen ray therapy.

The cases chosen were all proven by pathologic study to be malignant. They were: 2 cases of myelogenous leukemia, 1 of carcinoma of the stomach with belly wall metastases, 1 of melanosarcoma of the leg with metastases, 1 of squamous cell carcinoma of the tongue, 1 of fibrosarcoma of the leg, 1 of Hodgkin's disease, 1 of cancer of the lung, 1 of metastatic neck cancer, and 1 of postoperative breast cancer with metastases.

The serious problem of feeding large amounts of egg white to patients was overcome by special care in the preparation of the diet, since in the beginning of this study a more concentrated form of avidin was not available. To carry out these experimental clinical observations, a number of beds were set aside exclusively for patients undergoing this treatment, and 2 trained graduate nurses were especially assigned in order to check properly every phase of the treatment. The amounts of egg white fed the patients were empirical and arbitrary, but as nearly as possible the amount suggested by Sydenstricker in his experiments for the production of biotin deficiency. Each patient ate 36 to 42 egg whites per day with a general diet as free as possible from foods rich in biotin, along with a daily supplement of accessory vitamins and minerals.

Viewing these cases as a whole, we noted that the general condition of all was markedly improved. Instead of the usual increasing cachexia commonly noted in such advanced malignant cases, a general well-being was evident, with improved appetite and willingness to be up and about. This was especially noted in 2 cases (tongue and stomach) which, previous to the treatment, were apathetic, morose and constantly complaining.

Despite the large amounts of protein ingested, no apparent disturbances in general metabolic processes were noted, uremia did not occur in any case and only in 1 case was there a temporary increase in the blood cholesterol. There was no significant change in the blood counts. There was no effect on the white cell count in the 2 leukemia cases (Cases 1 and 6), but although the high white cell count persisted, there was a noticeable relief of general subjective symptoms with avidin therapy. Although biotin deficiency effects have been reported as occurring in humans, none of these cases showed any definite symptoms of biotin deficiency.

With regard to the effect on tumor growth, in the cancer of the tongue (Case 7), we noted definite recession of the tongue growth. The tongue lesion, which filled the whole buccal cavity and prevented ingestion of all foods except moderate amounts of liquid, has receded to such an extent that the tongue is now freely movable and the patient able to eat semi-solid food. At present he can talk so as to be understood, whereas before treatment, mumbling was the best he could do. This patient was treated solely by avidin therapy. The small submaxillary nodes felt at the beginning of the treatment have in no way changed in their size or extent.

* Aided by a special fund, obtained for us for this purpose through the efforts of Mr. William Laurence.

As already emphasized, while we felt that no definite conclusions could be drawn as to the therapeutic value *per se* of avidin, we nonetheless believed it worth while to continue carrying on our investigations.

One difficulty encountered has been that of determining the proper dosage of avidin required for controlling a specific malignant growth. At first we used as a daily dose of avidin, 36 fresh egg whites (about 126 gm.). Sydenstricker[18] in his experiments used 200 gm. of dried egg white powder, equivalent to 50 to 60 fresh egg whites. Whether or not a larger dose of egg white, avidin, is required to completely control malignant growth is still undetermined. We increased the amount of egg white to 42 per day and as far as can be observed there was little if any improvement in the results.

In March 1943, through the courtesy of Hoffmann-La Roche, Inc., we were able to secure a substantial amount of concentrated avidin and we have since then treated 1 case of cancer of the neck (Case 3), with a definitely proven, visible and palpable large metastatic squamous cell mass, solely with concentrated avidin. Each day this patient has been receiving 3 capsules of 666 mg. each of avidin, equivalent to a total of 2000 units per day. The diet was as near biotin-free as possible. As yet this patient has not exhibited any evidence of biotin deficiency. At first we noticed a decrease in the size and fixity of the tumor mass in the neck. Now after a period of 4 months and the ingestion of approximately 271,000 units of avidin concentrate, there is no evidence of tumor control or lessening of the neoplasia. The surface has broken down and involvement through the skin has taken place.

The 1 case of Hodgkin's disease (Case 4), a young woman 28 years of age, appears to have improved under egg white therapy alone. Although she still shows definite clinical evidence of the disease, she is about and working and in comparatively good condition, without complaints. While it is not, of course, entirely possible to attribute the improved condition of this woman solely to egg white therapy, nevertheless, we are not unwarranted in regarding egg white as having contributed towards her well-being and the inhibition of further advancement of malignant neoplasia.

The effect of avidin on radiation responsiveness is yet to be determined. However, the rapid response to Roentgen ray therapy in several cases suggests a definite influence of avidin. In 1 leukemia case, following avidin therapy, the radiation effect was definitely prolonged and the rise of white cell count controlled.

In the case of melanosarcoma of the leg and thigh with metastases irradiation after 3 months of egg white therapy caused complete disappearance of the clinical evidence of melanoma and has seemingly inhibited further extension or metastases.

In the lung cancer case, irradiation following prolonged egg white therapy appeared to produce rapid pulmonary changes and apparent resolution of part of the malignant lesion. However, this patient succumbed, probably to pulmonary hemorrhage (no autopsy being per-

mitted) 10 months after treatment and undoubtedly later than if no treatment at all had been given, or at best the usual course of Roentgen ray therapy alone.

Details of all cases treated and under supervision follow.

Case Studies. CASE 1. L.S., age 43, was admitted on August 24, 1942 complaining of a chronic cough of 5 to 6 years' duration which he attributed to his "sinus trouble." In 1938 blood-streaked sputum was noted, none since. In January 1942, following a cold, his cough became worse. Lost 12 pounds weight in 5 years. Because of continued cough he was admitted to the hospital.

Examination on admission revealed questionable enlargement of the spleen, 1 cm.; Roentgen ray of the chest revealed moderate sized areas of infiltration at the extreme right apex and the peripheral portion of the right 1st interspace. In the axillary portion of the right 2nd interspace is an infiltrated area which stretches towards the mediastinal shadow by fibrous strands which give rise to some honeycombing effect. Left lung showed slight apical pleural thickening. Emphysema both bases. The trachea was markedly deviated to the right along with the remainder of the mediastinal shadow, but this was probably due for the most part to the eccentric position of the patient which was repeated on all films. Blood count showed W.B.C. 100,000. Diagnosis of pulmonary tuberculosis and myelogenous leukemia was made.

Patient, starting on egg whites August 15, 1942, received 36 per day until December 4th. During the total of 112 days he received 4032 egg whites. From December 5th until June 2, 1943 patient received 42 per day until 7434 egg whites in 177 days were given. Thus this patient received a grand total of 11,466 egg whites in 289 days. The patient also received Roentgen ray therapy over the anterior spleen on February 18th, and June 2nd, 300 r given at each sitting. Condition controlled.

CASE 2. A.S., age 60, admitted August 18, 1942 complaining of cough productive of small amount of watery or mucoid sputum of 1 month duration. Three weeks before admission he began to sweat and developed pain in the right anterior chest. Weight loss of 25 pounds in 8 months. No wheeze, hoarseness or hemoptysis. Nocturia 6 to 8 times per night for past 6 years.

Examination at time of admission: Chest: decreased A.P. diameter, slight right apical lag. Lungs: dullness over upper lobe extending to 3rd rib anteriorly and 4th thoracic vertebra posteriorly. Absent breath sounds over this area, no râles. Rest of lungs clear. Nine sputum concentrates negative for tuberculosis. Roentgen ray examination of July 31, 1942 revealed: "Dense clouding in the medial two-thirds of the right upper lung field extending from the level of the 3rd rib anteriorly to the apex. Peripheral one-third is less densely clouded. Area is limited below by interlobar fissure which is convex upwards. Rest of lung fields are clear. Trachea is deviated somewhat to the right. There is some widening of the aortic shadow." Bronchoscopy on June 3, 1942 revealed: "Right upper lobe exceedingly difficult to identify. Eventually identified as a little crevice, its lumen completely occluded by thickened mucosa and also by compression from the outside. On the proximal lip of the right upper lobe there is some rough tissue."

Pathologic examination of February 12, 1943 revealed squamous cell carcinoma of the bronchus.

Patient was started on egg whites August 10, 1942, receiving 36 per day until December 15, 1942. During 126 days he received 4536 egg whites. Starting December 29, 1942, patient received 42 per day until January 26, 1943. In a total of 35 days he received 1470 egg whites. Egg whites were again resumed on February 18, 1943, received 8 per day until June 2nd. He received 840 egg whites in 105 days. Thus since August 10, 1942 the patient received 6846 egg whites in 266 days.

From October 26 to November 24, 1942 Roentgen ray therapy was given to the anterior right mediastinum—3000 r, and to the posterior right upper chest—3000 r. From February 18 to April 2, 1943 Roentgen ray therapy was

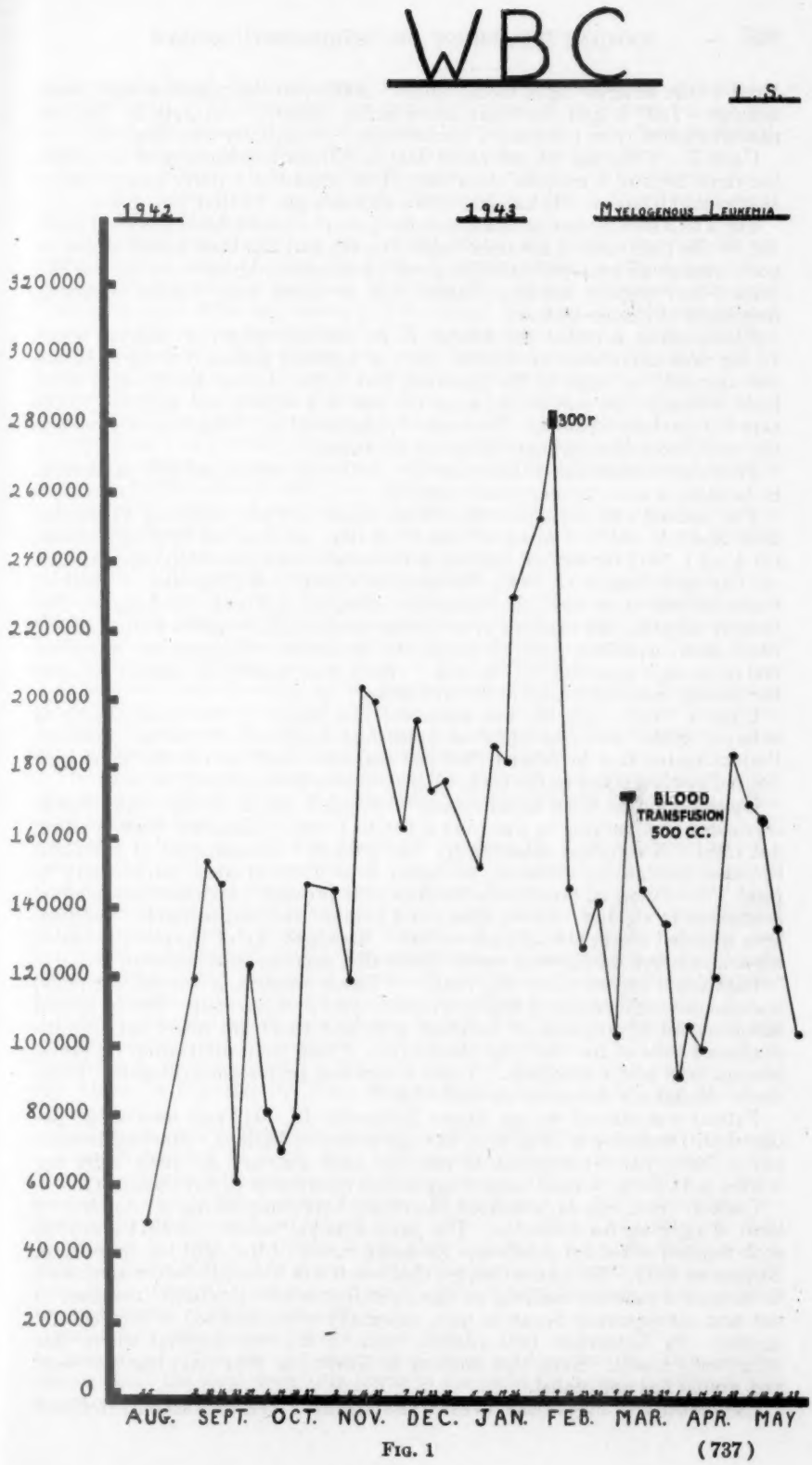

WBC
L. S.
1942
1943
Myelogenous Leukemia
320000
300000
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
300r
BLOOD TRANSFUSION 500 CC.
AUG. SEPT. OCT. NOV. DEC. JAN. FEB. MAR. APR. MAY

Fig. 1

given to the anterior right mediastinum—3000 r, to the posterior right mediastinum—2100 r, and the right lower axilla—3000 r. On July 5, 1943 the patient expired from pulmonary hemorrhage. No autopsy was obtained.

CASE 3. T.B., age 64, admitted March 6, 1943 complaining of a mass in the right neck of 3 months' duration. The patient is a fairly heavy user of alcohol and tobacco. He had gonorrhea 45 years ago, treated, lues denied.

For 2 to 3 months before admission the patient states a mass has been growing on the right side of his neck below the ear and has been accompanied by occasional small hemoptyses. The growth has been progressive to the size of a walnut and slightly tender. Patient has no chest pain, fatigue, dyspnea, dysphagia or change in voice.

Examination revealed the tongue to be smooth, posterior pharynx clear. In the neck there were no dilated veins or palpable nodes. On the right side just beyond the angle of the mandible and below the ear there was a solid, hard, irregular and non-tender mass the size of a walnut, not attached to the skin but movable below it. No signs of inflammation. Diagnosis of cancer of the neck, secondary, primary unknown was made.

Pathologic diagnosis of February 26, 1943 was squamous cell carcinoma, metastatic in neck, primary site unknown.

The patient was started on egg whites March 6, 1943, receiving 42 per day until April 1, 1943. During a total of 26 days he received 1092 egg whites. On April 1, 1943 the patient was started on avidin capsules, receiving 3 capsules per day until August 15, 1943. He received a total of 408 capsules of which 42 contained 660 units each; the remainder contained 666 units per capsule. The patient received 408 capsules in a 136-day period; 336 capsules contained 666 units each, equalling 223,776 units, the remainder, 42 capsules, contained 660 units each equalling 27,720 units. Thus from April 1 to August 15, 1943 the patient received a total of 271,476 units.

CASE 4. G.C., age 28, was admitted November 9, 1942 complaining of enlarged gland and hoarseness of voice and cough of 3 months' duration. Patient stated that in August 1942 she began to cough and at the same time noticed swollen gland in the neck. Voice became intermittently hoarse.

Examination at time of admission revealed 3 glands in the right supraclavicular area varying in size from a pea to 1 cm. in diameter, discrete, firm, not fixed. No axillary adenopathy was present. Examination of the chest revealed mediastinal dullness percussed over widened area, particularly to right. No abnormal pulmonary findings were present. Abdomen revealed no tenderness or rigidity. Liver, spleen and kidneys were not palpable. Inguinal area revealed small, shotty node on left. Roentgen ray of the chest revealed several enlarged mediastinal nodes bilaterally, superior mediastinum.

Pathologic report (May 10, 1943): "Tissue consists of several lymphoid nodules the architecture of which is distorted by fibrous tissue. The lymphoid tissue shows hyperplasia of reticular cells and there are many large multinucleated cells of the Dorothy Reed type. There is an infiltration by polys, plasma cells and eosinophils. There is marked perivascular fibrosis. Diagnosis: Hodgkin's disease of cervical node."

Patient was started on egg whites November 16, 1942 and received 36 per day until December 4, 1942, *i. e.*, 648 egg whites in 18 days. Starting December 5, 1942, patient received 42 per day until January 30, 1943, 2394 egg whites in 51 days. Grand total of egg whites received in 75 days was 3042.

CASE 5. S.S., age 44, admitted March 25, 1942 complaining of an unhealed ulcer of right leg for 4 months. The patient had a "stroke" in 1914 and 1915 with residual left-sided paralysis. He had a tumor of the right leg removed in November 1941. The patient stated that about 4 or 5 months before admission he noticed a painless swelling on the right foot which gradually increased in size and subsequently began to pain, especially when handled or accidentally injured. In November 1941 patient went to Harlem Hospital where this lump was excised. Since this excision in November 1941 pain has increased and wound has not healed.

Examination of the patient revealed the cremasteric reflexes absent, Hoffman

positive right hand, Babinski negative. The left leg was thinner and weaker than the right. The dorsum of the right foot revealed an ulcer 4 x 8 cm. the contents of which moved with movement of the ankle. This was reddened, raised, swollen and ulcerated. Right inguinal nodes were palpable.

Pathologic Examination (Harlem Hospital): Spindle cell sarcoma. Pathologic report from Bellevue Hospital (December 7, 1942): Spindle and giant cell sarcoma of the foot.

The patient was started on egg whites March 27, 1942, receiving 36 egg whites per day until October 24, 1942 (7560 egg whites in 210 days). Egg whites were resumed December 4, 1942, receiving 42 egg whites per day until March 23, 1943 (4904 egg whites in 112 days). On April 1, 1943 the patient started on egg whites again receiving 42 per day until May 1, 1943 (1260 egg whites in 30 days). Egg whites were again resumed on May 28, 1943 and he received 42 per day until June 22, 1943 with the exception of 6 days. In the total of 19 days he received 798 egg whites. Thus from March 27, 1942 until June 22, 1943 the patient received a total of 14,522 egg whites in 371 days.

From June 2 to June 29, 1942 Roentgen ray therapy was given to the medial right leg—4230 r. From February 4 to March 24, 1943 Roentgen ray therapy was given to the anterior right foot—6000 r.

Because of combined contracture of the knee and distress amputation was performed on July 9, 1943. After amputation the patient has markedly improved and there is no evidence of recurrence or metastases.

Case 6. V.H., age 68, was admitted August 15, 1938 complaining of bleeding from varicose veins of left foot. Examination revealed the spleen to be 10 cm. in mid-clavicular line. Two plus edema of ankles and varicose veins of both legs and on lateral side of left ankle a varix was sutured. Blood count showed typical myelogenous leukemia (W.B.C. 282,000).

Patient was started on egg whites September 3, 1942, receiving 36 egg whites per day until December 4, 1942 (3276 egg whites in 91 days). From December 5, 1942 until March 31, 1943 (116 days) she received 4872 egg whites. Thus she received a grand total of 8148 egg whites in 207 days.

The patient was also given Roentgen ray therapy over the anterior spleen on January 2, March 31 and May 28, 1943, receiving 300 r at each sitting. Her condition steadily improved.

Case 7. R.S., age 50, was admitted January 22, 1940 complaining of a rash on the right leg, spreading, of 6 months' duration. The patient stated that 6 months before admission she developed brown spots on the lower right leg which seemed to start from one brown pigmented area. She was admitted to the hospital and a diagnosis of Kaposi's disease was made. Biopsy was performed and reported "malignant melanoma." Examination revealed right inguinal adenopathy present, 2 cm. nodes, numerous oval, brownish, papular lesions scattered over the lower portion of the right posterior leg.

Patient was started on egg whites August 19, 1942 and received 36 egg whites per day until December 4, 1942 (3852 egg whites in 107 days). From December 4, 1942 to April 15, 1943 she received 42 egg whites per day (5502 egg whites in 1931 days). Thus she received a total of 9354 egg whites in 238 days.

Pathologic report (October 15, 1942): Malignant melanoma of the thigh.

From November 16 to 20, 1942 Roentgen ray therapy to right thigh, area 1, 500 r (superficial) and to right thigh, area 2, 500 r (superficial). From January 4 to 8, 1000 r; from January 18 to March 2, 1943, Roentgen ray therapy to single lesion on lateral knee 1500 r; to right heel 1500 r; to right thigh area 1, 1500 r; to right thigh area 2, 1500 r; to right thigh area 3, 1200 r. From March 3 to April 9, 1943 Roentgen ray therapy to right abdomen, 800 r; to right thigh areas 1 and 2, 1500 r; to right thigh area 3, 1500 r; to inner aspect of right knee 1500 r.

Patient was discharged home April 15, 1943.

On May 17, 1943, patient returned to clinic for observation. Examination showed that the local melanotic lesion in the right thigh had completely disappeared. No evidence of recurrence or extension.

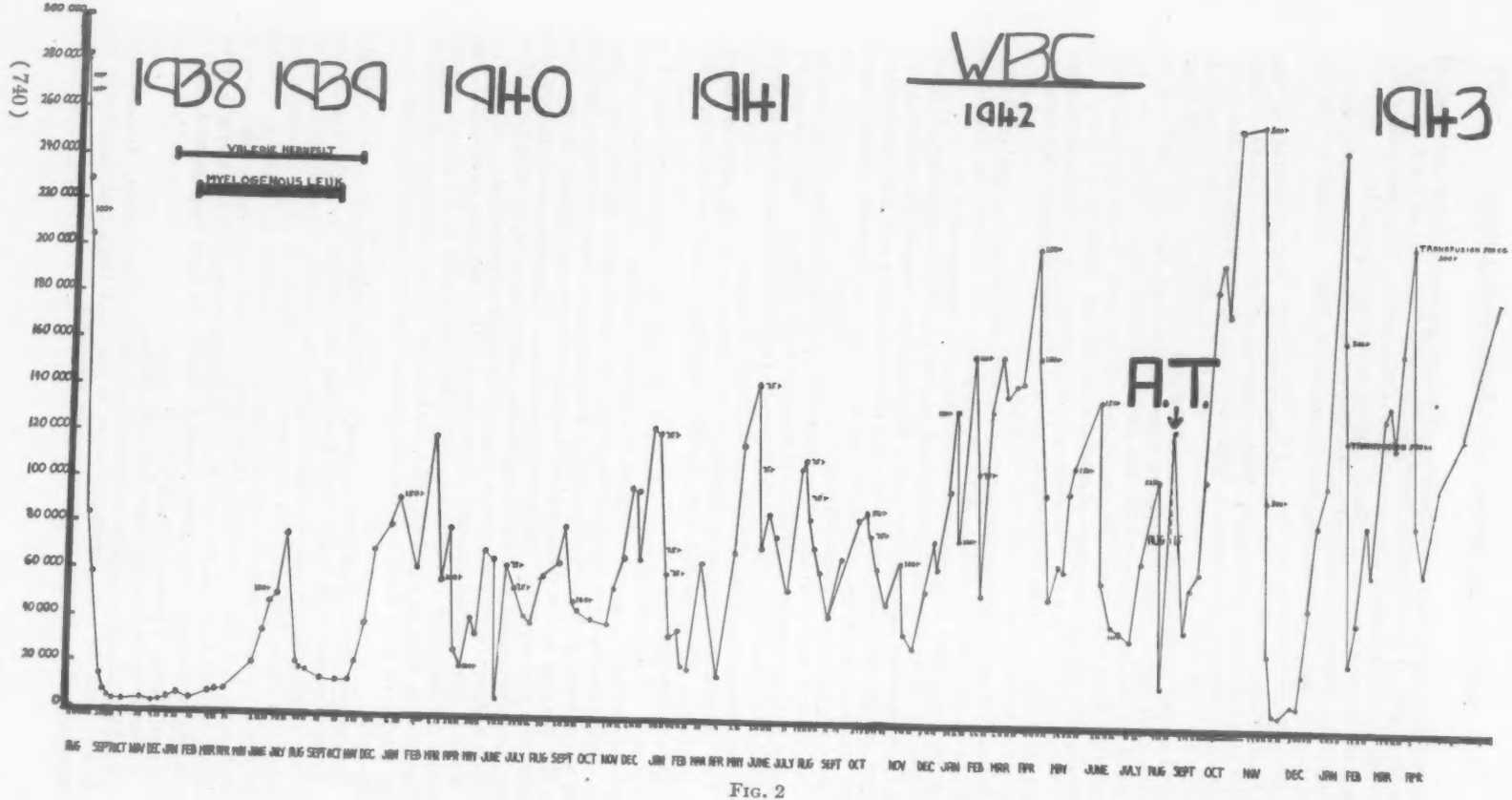

(740)
1938
1939
1940
1941
WBC
1942
1943
VOLEDIE HERBERT
MYELOGENOUS LEUK
A.T.
TRANSFUSION 200 cc.

FIG. 2

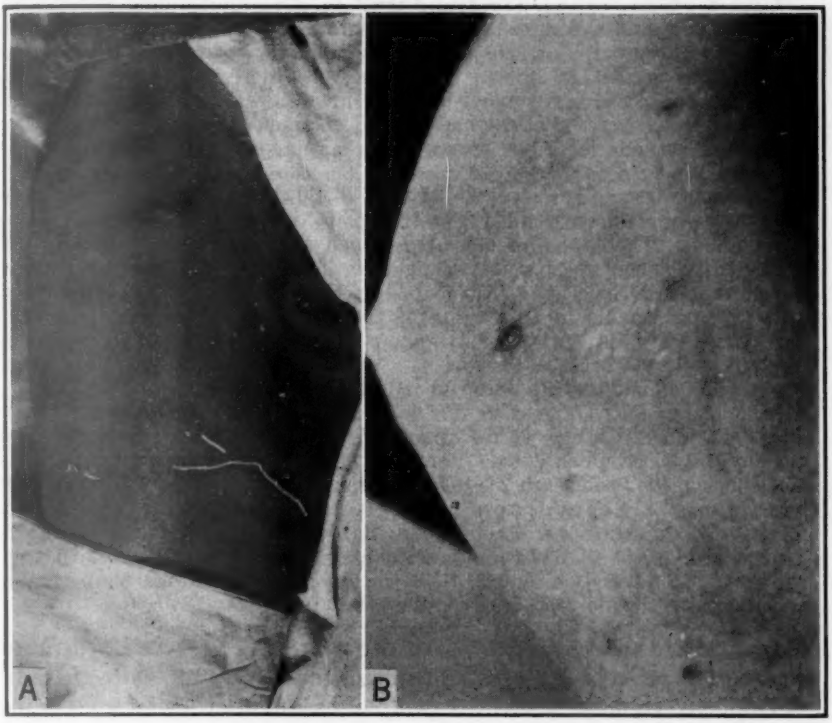


FIG. 3.—*A*, Before treatment; *B*, after treatment.

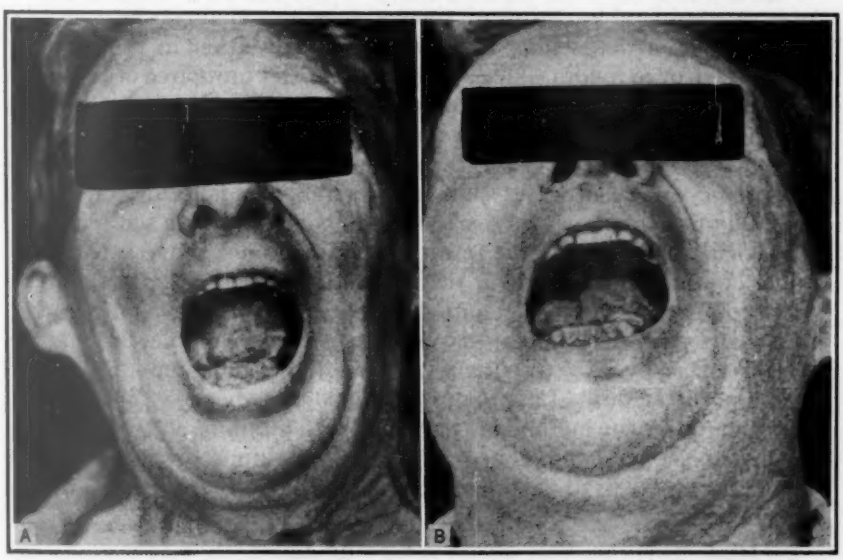


FIG. 4.—*A*, Before treatment; *B*, after treatment.

CASE 8. G.M., age 64, admitted August 17, 1942 complaining of difficulty in swallowing and talking of 4 months' duration and lesion on tongue of 6 months' duration. Six months previous to admission patient was aware of a small lesion on the left side of his tongue, posteriorly. Two months later patient began to have progressive difficulty in swallowing and talking and had pain in the left neck. Patient had noticed enlargement and recession of the mass in his tongue for a few weeks before admission. No smoking for past 25 years.

Local examination revealed the left half of the tongue occupied by a large fungating mass which extended from the lips to the posterior portion, crossing the midline. There was an ulcerated trench adjacent to the lower row of teeth, at the side of the tongue. Tongue was fixed and could not be extruded beyond the lower incisors. No acute infection was present. There was a solitary hard nodule in the region of the right submaxillary gland about 2 x 2 cm. A firm left tonsillar gland about 2 x 1 cm. was present with marked tenderness in the neck just below it. No further adenopathy was present. Patient had offending teeth removed on left side.

Pathologic report (August 19, 1942): Squamous cell carcinoma of tongue.

Patient started on egg whites August 15, 1942 and received 36 egg whites per day until December 4, 1942 (total of 111 days—3996 egg whites). From December 5, 1942 to March 28, 1943, he received 42 egg whites per day (4788 egg whites in 114 days). April 5, 1943, patient resumed egg whites again, receiving 42 egg whites per day until July 8, 1943 (3790 egg whites in 90 days). Thus since August 15, 1942 the patient received a grand total of 12,564 egg whites in 315 days. On July 8, 1943, the lesion was more than 50% smaller and the patient could talk clearly and swallow freely.

Discussion and Conclusions. We can state that as yet no definite cure of cancer has been effected through the use of egg white therapy as employed by us in a selected group of cases. As the diet given contained substantial quantities of milk which may have been a source of readily absorbable biotin, this may have been one reason for the unfavorable results obtained. But while no definite conclusions can as yet be predicted on our results, based on a large number of cases over a considerable period of time, we believe that avidin must be given in larger doses than those we employed, either in the raw egg white state or in avidin concentrate with the diet quite free of biotin.

Whether the neutralization by avidin of the cell-growth stimulating biotin accounts for the effects already noted cannot be stated definitely, but the fact that the customary progressive extension of the malignancy in several cases is absent inevitably leads to the conclusion that avidin therapy may have played a pronounced rôle in such cases.

Notwithstanding that the results obtained do not prove substantial value of egg white treatment of neoplastic diseases, it would not be proper to draw therefrom any definite conclusions evaluating this method of treatment. This is because we were unable to produce biotin deficiency in our patients even by the employment of pure avidin in the amount of approximately 2000 units per day. It remains now to improve the method of treatment with vitamins so as to balance the diet to such a degree that by addition of avidin a biotin deficiency would be created. The proper dosage for avidin still waits to be determined.

Dr. Milton Zurrow who ably assisted in the early stages of the work concluded his internship in our service some months ago, prior to the conclusion of the study, and his place was taken by Dr. John Moseley. The author's thanks are extended to both.

For the financial aid which made this research possible we are indebted to Mr. William Laurence of *The New York Times*, and to the Carter Nicholas and Burden Funds. Further support from these sources enables us to continue the experiment and we expect to have further results to report at a future date.

REFERENCES

1. Bateman, W. G.: J. Biol. Chem., **26**, 263, 1916.
1a. Bateman, W. G.: Am. J. Med. Sci., **153**, 841, 1917.
2. du Vigneaud, V., Spangler, J. M., Burk, D., Kensler, C. J., Sugiura, K., and Rhoads, C. P.: Science, **95**, 174, 1942.
3. du Vigneaud, V., Melville, D. B., Gyorgy, P., and Rose, C. S.: Science, **92**, 62, 609, 1940.
4. Eakin, R. E., McKinley, W. A., and Williams, R. J.: Science, **92**, 224, 1940.
5. Eakin, R. E., Snell, E. E., and Williams, R. J.: J. Biol. Chem., **140**, 535, 1941.
6. Friedberger, E.: Deutsch. Med. Wchnschr., **52**, 1760, 1926.
7. Goldfeder, A.: Personal communication.
8. Gyorgy, P., Mellville, D. B., Burk, D., and du Vigneaud, V.: Science, **91**, 243, 1940.
9. Gyorgy, P., Rose, C. S., Eakin, R. E., Snell, E. E., and Williams, R. J.: Science, **93**, 477, 1941.
10. Kaplan, I. I.: Radiol. Soc. North America Meet., Chicago, December, 1942.
11. Koeg, R., and Toennis, B.: Ztschr. f. physiol. Chem., **243**, 43, 1936.
12. Laurence, W. L.: Science, **94**, 88, 1941.
13. Maignon, F., and Chahine, M. A.: Compt. rend. Acad. d. sc., **166**, 918, 1918.
13a. Maignon, F., and Chahine, M. A.: Compt. rend. Soc. de biol., **108**, 929, 1931.
14. Parsons, H. T., and Kelly, T.: Am. J. Physiol., **104**, 159, 1933.
15. Pollack, M. A., Taylor, A., Woods, A., Thompson, R. C., and Williams, R. J.: Cancer Research, **2**, 748, 1942.
16. Rhoades, C. P., and Abels, J. C.: J. Am. Med. Assn., **121**, 1261, 1943.
17. Rohdenburg, G. L.: J. Cancer Res., **3**, 193, 1918.
18. Sydenstricker, V. P., Singal, S. A., Briggs, A. P., and de Vaughn, N. M.: J. Am. Med. Assn., **118**, 1199, 1942.
19. West, P. M., and Woglom, W. H.: Science, **83**, 525, 1941.
20. West, P. M., and Woglom, W. H.: Cancer Res., **2**, 324, 1942.

CONCENTRATION OF RED BLOOD CORPUSCLES CONTAINING LABELED PHOSPHORUS COMPOUNDS IN THE ARTERIAL BLOOD AFTER THE INTRAVENOUS INJECTION*

Preliminary Report

By Gustav Nylin
and
Mignon Malm
Stockholm, Sweden

(From Sabbatsbergs Hospital and Wenner-Gren Institute, Stockholm)

To the Memory of Soma Weiss

Since the time of Stephen Hales, but few until very recently have studied the velocity of the blood flow in man. The most notable studies were made by H. Blumgart and Soma Weiss,[1] 1927–1928, who introduced a new method of measuring the velocity of the blood flow. They injected radium C intravenously and, with the aid of the Geiger counting-chamber, determined the circulation time in different parts

* We wish to express our appreciation to Professor Hevesy for his constant advice and encouragement and especially Professor Rundström, who has generously placed at our disposal his laboratory. We also wish to express our hearty thanks to Prof. M. Siegbahn for the gift of radioactive phosphate.

of the circulation. Thanks to many published contributions they founded our knowledge of the velocity of the blood flow in normal and pathologic conditions, especially in compensated and decompensated heart cases. Their results have been confirmed by Tarr, Oppenheimer and Sager,[9] Winternitz, Deutsch and Brüll,[10] Nylin,[7] Nylin and Malmström,[8] and others.

With the aid of other test substances, especially decholin, the fundamental investigations of Blumgart and Weiss have produced results of practical importance. We now know that a prolonged circulation time in heart cases means a slow circulation and is a criterion of decompensation. But Nylin[7] and Nylin and Malmström[8] have shown that it is not only the slow circulation in decompensation that explains the prolonged circulation time, but that there is another factor that must be taken into consideration. Nylin[7] has shown that the amount of the residual blood in the heart plays a dominating rôle in prolonging circulation time. There are many heart cases without any signs of decompensation, where all congestive phenomena are absent, with normal venous pressure and no congestion of the lungs, but with dilatation of the heart and a pathologically great heart volume, in which the circulation time is markedly prolonged. At the same time the duration of the taste sensation of decholin is greatly prolonged in those cases. Nylin[7] has postulated, and found in fact, that the prolonged circulation time and the long duration of the taste sensation in compensated heart cases are closely correlated with the increase of residual blood, as would be supposed from the pathologically increased heart volume. The determination of the velocity of blood by the aid of decholin is a subjective method and gives no real quantitative information. For the purpose of reaching a better understanding of this problem, Nylin and Hevesy, in Copenhagen, have introduced a new method for determining the red blood corpuscle contents. Thanks to Hevesy's generous permission, one of us (M. M.) has learned in his laboratory the technique of labeling the corpuscles and of measuring the activity with the aid of the Geiger counter. In Stockholm, Malm has introduced the method in Wenner-Gren's Institute, and Nylin has applied it in clinical research.

Experimental Procedure. Hitherto in experiments performed on human objects the indicator is injected directly in the blood. By analysis of the collected blood samples a measure of the amount of indicator in the plasma is obtained, because a permeation of indicator in the blood corpuscles during the short times required by the experiments could be neglected. After a strong rising at first of the concentration of the indicator in the first blood samples, the concentration is rapidly falling in the following samples not only due to the rapid mixing of the indicator with the blood but also due to the rapid resorption of the indicator by the tissues in the body.

This fact is also pointed out by Gerlach *et al.*,[2] who has determined the time for circulation of the blood in man with the aid of Th X. In the mentioned work this also appears from a graphic registration of the lapse of time for the mixing of the indicator with the blood.

According to a method to determine the content of the red blood corpuscles worked out by Hevesy and Zerahn[6] this source of error is eliminated. This modification of the earlier described procedure[3] was worked out just in view of a possible clinical application of the method.

By the method mentioned above, both plasma and blood corpuscles are labeled, but only the amount of indicator of the latter is determined after the injection. This method has been followed in the present work.

Five ml. of blood are removed from the patient, placed in a small flask containing a negligible weight of sodium phosphate labeled with radioactive phosphate. The flask is shaken in a thermostat for 2 hours at 37° C. After this time the distribution coefficient of labeled ions between corpuscles and plasma of equal weight has reached a value of about 0.9.[4]

Three ml. of the blood containing the labeled corpuscles are then reintroduced into a vein in the arm of the patient. Before the injection, a cannula, to which was attached a tap with a rubber tube, was introduced into an artery of the other arm, which made it possible to collect the blood samples only a few seconds after the injection. The blood is collected in small glass tubes—about 2 or 3 ml. in each.

The samples were then centrifuged, the plasma is removed and about 0.5 gm. blood corpuscles are weighed in. The blood corpuscles are ashed with sulfuric and nitrogen acid, a known amount of inactive sodium phosphate is added and the phosphate is precipitated as ammonium magnesium phosphate.[5] The obtained precipitates are measured with the aid of a Geiger counter.

The strength of the radioactivity in the different samples is worked out per gram and is expressed in % of the value of the strongest sample.

Possible errors such as adhesion of active plasma to the corpuscles and how properly the label of the corpuscles is conserved are discussed by Hevesy and Zerahn.[6]

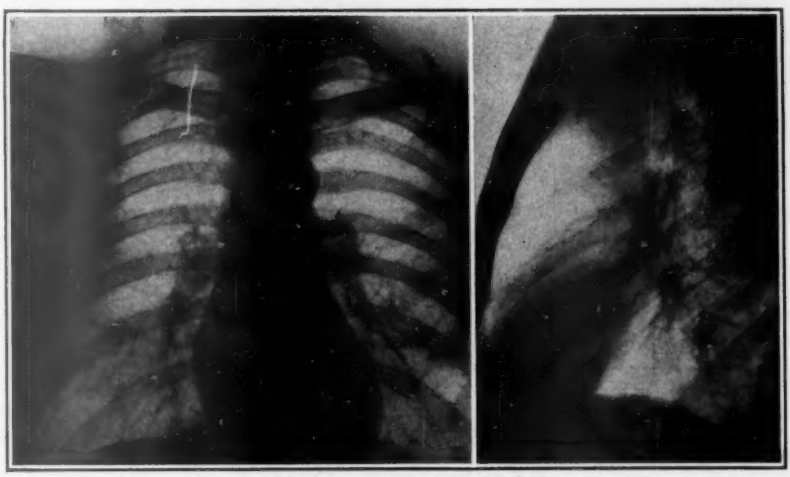


FIG. 1.—Heart volume in a healthy person in a standing position. Volume 620 ml., *i. e.*, 320 ml./m² of body surface. (Case 1.)

Results. Since November, 1942 we have applied the method in some clinical cases in order to find out whether the prolonged circulation time and the prolonged duration of the taste sensation, determined by the aid of decholin, in cases with heart dilatation, were correlated with a prolonged relative activity of the arterial blood after injection of red corpuscles containing labeled phosphorus compounds. Examples of these results follow.

CASE 1. Healthy man, 27 years of age. Heart examination normal. Blood pressure 120/80. Venous pressure 7.5 cm. Velocity of circulation,

determined with decholin: first taste sensation after 15 seconds, disappearance of this sensation after 34 seconds, after intravenous injection of decholin. Roentgen ray of the heart: Heart configuration normal. Heart volume 620 ml., *i. e.*, 320 ml./m² of body surface (Fig. 1).

TABLE 1.—VALUES OBTAINED IN CASE 1

Time after injection, sec.	Relative activity	Time after injection, sec.	Relative activity	Time after injection, sec.	Relative activity
5	0	33	19.7	120	40
7	0	35	47	180	37.5
9	0	37	46	240	41.5
11	0	39	45	300	37.5
13	21.6	41	47	600	33
15	66	43	47	900	34
17	86.5	45	43	1800	40
19	100	47	38.5		
21	96	49	40	1 day	47
23	95	51	41.5	3 days	13.5
25	73	53	38.5	4	12
27	57	55	35.6	5	10
29	42	57	36.5	6	6
31	40	60	37.5	7	8

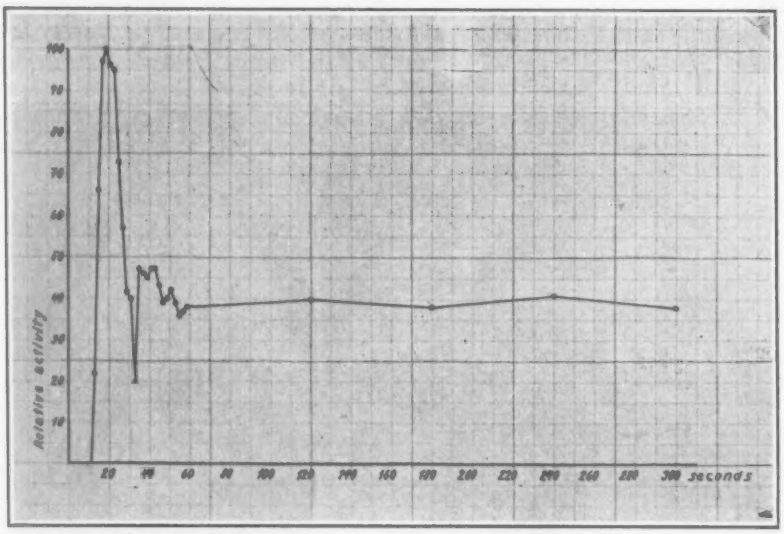


CHART 1.—Relative activity of the blood in the brachial artery as a function of time in a healthy person. (Case 3.)

Intravenous injection of about 10 μ C. in the right antecubital vein was made early in the morning with the subject in a horizontal position. The subject had not taken any food since the previous evening and had not been out of bed in the morning before the test. During the injection in the right arm and during the puncture of the left brachial artery, both arms were held in a quite horizontal position. The puncture of the artery was made, before the intravenous injection in the right arm, with a syringe cannula of the size we use for venous pressure determinations. A tap was attached to the needle, and to this a rubber tube. Cannula and rubber tube had been moistened with heparine to prevent blood clotting. Immediately after the labeled corpuscles had been injected very quickly (in about a second), the tap of the cannula in the artery was opened, and small glass tubes moistened with heparine and

placed in a special stand, were filled up to about 2 ml. each with blood from the artery. It took about 2 seconds for each tube. The blood in the tubes was then analyzed for its activity. The values of the relative activity are inserted in Table 1 and also in Chart 1. From this diagram it can be seen that the labeled corpuscles make their first appearance in the arterial blood about 13 seconds after the intravenous injection, and that the relative activity increases to its highest point 19 seconds after the injection and then it rather quickly decreases to a minimum 33 seconds after the injection. This means that there is a strong correlation between the measurements of the velocity made with decholin, when the first taste sensation occurred 15 seconds after the injection and disappeared after 34 seconds, and the relative activity of the arterial blood. In the diagram there is a new peak in the curve after 35 to 43 seconds as a result of recirculation. After that time the curve rather quickly decreases to a constant level, which persists for more than 300 seconds.

FIG. 2.—Heart volume in a case of mitral stenosis with extreme bulging of the pulmonary artery. Heart volume 2.490 ml., *i. e.*, 1.600 ml./m² of body surface. (Case 2.)

CASE 2. Woman 51 years old. Diagnosis: Mitral stenosis without congestion with severe heart dilatation. Blood pressure 170/110. No symptoms of congestion. Venous pressure 8 cm. Velocity of the blood flow determined with decholin: first taste sensation after 20 seconds; disappearance of the bitter taste after 90 seconds. Roentgen ray of the heart shows a generalized cardiac enlargement with pronounced bulging of the pulmonary artery. Heart volume 2.490 ml., *i. e.*, 1.600 ml./m.² of body surface. (Fig. 2.)

The results of the blood velocity studies with labeled corpuscles are seen in Table 2 and Chart 2. From Chart 2 it is seen that the relative activity of the arterial blood in the left brachial artery increases slowly to a maximum 25 seconds after the injection of the labeled red corpuscles in the right antecubital vein, and that then during a much longer time than in the normal case, there is a rather high level of the relative activity of the arterial blood—more than 120 seconds—and that during a time of 30 to more than 60 seconds there are small, irregular peaks in the curve. After 180 seconds the curve reaches a more constant level, which is maintained for more than 300 seconds after the injection.

Comment. From these preliminary investigations it is seen that, in a normal person with a normal heart volume, the velocity of the blood flow—determined with the aid of red corpuscles containing labeled phosphorus compounds—is strongly correlated to the circulation time

and the duration of the taste sensation after the injection of decholin. To some degree this correlation also holds good in the case of heart dilatation, and Chart 2 clearly shows that it takes a remarkably long time for the activity in the arterial blood to reach a constant level after the injection. In the case of heart dilatation without signs of congestion this slow decrease of the first part of the curve is probably

TABLE 2.—VALUES OBTAINED IN CASE 2

Time after injection, sec.	Relative activity	Time after injection, sec.	Relative activity	Time after injection, sec.	Relative activity
5	0	31	76	57	79
7	0	33	76	59	76
9	3	35	85	61	73.5
11	10.5	37	83	63	72.5
13	17	39	83	65	78
15	22.5	41	72	67	75
17	30	43	92	120	68
19	42	45	88	180	56.5
21	45	47	78	240	55.5
23	65	49	70	300	56
25	100	51	82	360	59.5
27	65	53	74	420	55
29	62	55	72.5	480	53

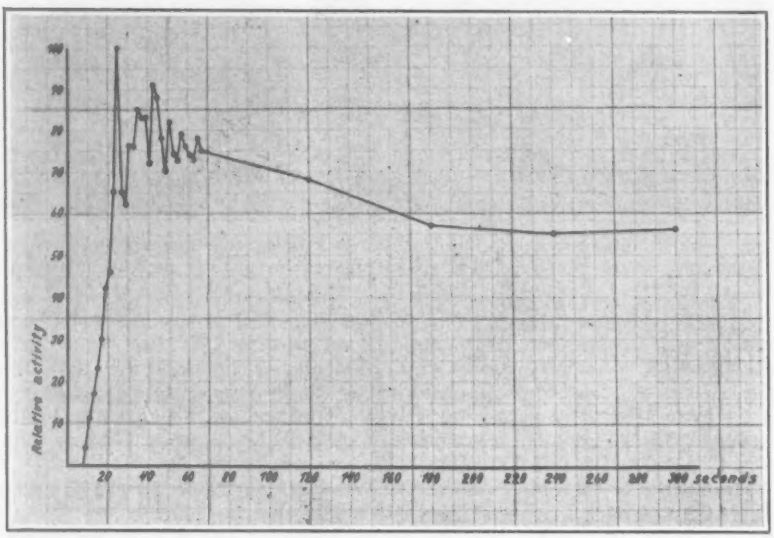


CHART 2.—Relative activity of the blood in the brachial artery as a function of time in a case of heart dilatation without congestion. (Case 2.)

to be explained by a great amount of residual blood in the heart and probably by the mixture of the injected labeled corpuscles with the residual blood not being so homogeneous and sudden as in a normal case. The irregular peaks of the curve in the case of heart dilatation also speak in favor of the assumption that, with a high amount of residual blood, the mixing of the blood in the heart takes a much longer time than in a normal subject. After this preliminary report,

it seems worth while to make further studies—which are actually proceeding in my laboratory—to gain more information about the amount of the residual blood in different heart cases. There seems to be some evidence for the assumption proposed by Nylin that the velocity of the blood flow and the prolonged circulation time are determined not only by the degree of decompensation, but probably also to a great extent by the amount of the residual blood in the heart.

Summary. 1. Hevesy has introduced a method for the determination of the erythron of the rabbit in a simplified form.

2. We have applied this method to man, *i. e.*, to healthy persons as well as to patients with heart dilatation.

3. There seems to be a correlation between the amount of the residual blood in the heart and the relative activity in the arterial blood of labeled red corpuscles determined at certain fixed points after intravenous injection of these corpuscles.

REFERENCES

1. Blumgart, H., and Weiss, S.: J. Clin. Invest., **4**, 15, 149, 173, 199, 389, 399, 1927.
2. Gerlach, J., Wolf, P. M., and Born, H. J.: Naunyn-Schmiedebergs Arch., **199**, 83, 1942.
3. Hahn, L., and Hevesy, G.: Acta physiol. Scand., **1**, 3, 1940.
4. Hahn, L., and Hevesy, G.: Acta physiol. Scand., **3**, 193, 1942.
5. Hevesy, G.: Ann. Rev. Biochem., **9**, 641, 1940.
6. Hevesy, G., and Zerahn, K.: Acta physiol. Scand., **4**, 376, 1942.
7. Nylin, G.: Nord. med. Ark., **10**, 1139, 1941.
8. Nylin, G., and Malmström: Cardiologia, **5**, 333, 1941.
9. Tarr, L., Oppenheimer, B. S., and Sager, R. V.: Am. Heart J., **8**, 766, 1933.
10. Winternitz, Deutsch and Brüll: Med. Klin., **27**, 986, 1931.

THE EVALUATION OF ALCOHOL LUMBAR PARAVERTEBRAL BLOCK IN PERIPHERAL VASCULAR DISEASE

By Gamliel Saland, M.D.
PHYSICIAN-IN-CHARGE, OF PERIPHERAL VASCULAR DISEASE
NEW YORK, N. Y.
AND
Capt. Charles Klein, M.C., A.U.S.

(From the Department of Peripheral Vascular Diseases, the Bronx Hospital)

The use of alcohol to produce block of the sympathetic ganglia was first introduced in this country by Swetlow[5] in 1923. Since then, various workers[4,6] in the field of peripheral vascular diseases have used this procedure to induce vasodilatation in the lower extremities and obtain relief from ischemic symptoms and signs.

No one has as yet determined objectively how long this vasodilatation exists. White[7] mentions that the effects of alcohol lumbar paravertebral block rarely lasts longer than 6 months.

In the past, particularly in the cases of angina pectoris, the evaluation of the effect of such injections has been made according to the patient's subjective feeling and, as in other evaluations, the patient's symptoms are unreliable criteria for determining the efficacy of a therapeutic procedure. It is well known that symptoms of vascular

disease may be relieved spontaneously, and so we thought it would be important for us to know by an objective method exactly how long one may expect the vasodilatation in the lower extremities to last after the injection of the lumbar vertebral ganglia with alcohol.

White[9] has shown both experimentally and in humans that, as a result of injection of 5 cc. of alcohol into tissues, an area of necrosis 1 cm. in diameter will be produced. If this necrotic area should involve the exact spot of the sympathetic ganglia, then it is conceivable that the effect of the injection might last forever.

We therefore tried to determine objectively: (1) exactly how long one may expect vasodilatation effects to last after alcohol paravertebral block in the lumbar region; (2) whether neuritis is produced by such a procedure, and if so, how often, how severe, and how long such neuritis might last; (3) whether the amount of alcohol used was a factor in producing vasodilatation or neuritis; (4) whether the use of novocaine in sweet almond oil would reduce the incidence of neuritis;* (5) incidentally, we tried to determine if claudication time would be altered by such therapy.

Procedure. *Material.* The patients studied were those who applied to the vascular clinic for relief of symptoms, and comprised a total of 16 patients. The types of cases were as follows: 1 phlebitis, 1 scleroderma, 1 thromboangiitis obliterans and 13 arteriosclerosis obliterans. These cases were chosen because it was determined previously, by peripheral nerve block with novocaine, that the extremity to be treated could vasodilate up completely.[1] These patients, therefore, served as excellent controls, for if our technique in doing the paravertebral block was correct, these patients should dilate up to 31° C.

Using the technique described by previous workers,[4,6] we injected the regions of the first, second and third lumbar vertebral ganglia. We divided the series into 3 groups.

Group I. Six cases: We used 2% novocaine followed by 5% novocaine in sweet almond oil, and this in turn by 1 cc. of 100% alcohol.

Group II. Four cases: 2% novocaine followed by 1 cc. of 100% alcohol.

Group III. Six cases: 2% novocaine followed by 3 cc. of 100% alcohol.

The blocks were performed at the clinic, the patients receiving no sedation. The patient was in the prone position during the block, with a pillow under the abdomen. The lower extremities were exposed from the thigh to the toes. The patient was kept in the prone position for about ½ hour after the block and then turned over on the back. Skin surface temperature readings† were taken 1 hour before injection to allow the skin temperature to stabilize. Readings were taken at intervals for a period of 2 hours after the block, at the end of which time the patient was allowed to leave the clinic.

Skin surface temperature readings were taken bilaterally: (1) at the base of the nail, on the dorsum of the big toe; (2) the mid-sole region of the foot; (3) the external malleolus; (4) the head of the fibula.

Follow-up skin surface temperature readings were done at various intervals; at first 3 days, and subsequently at longer intervals. A temperature difference of 2° C. in corresponding areas of extremities was considered significant. When there was no further significant difference in temperature in corresponding areas, the vasodilating effect of the injection was taken to have stopped, and the follow-up was ended.

* The use of 2% novocaine in sweet almond oil was suggested by Dr. Sidney Gross, to whom we are indebted for the demonstration of the technique of lumbar paravertebral block.

† The Taylor Dermatherm was used throughout our experiments.

When taking the follow-up readings, the patient was seated with the legs in the horizontal position, and the lower extremities were exposed to room temperature for 1 hour, at the end of which time readings were taken.

We attempted to keep the room temperature constant at any one sitting, but the room temperature at different times was as high as 26.6° C., and as low as 18.6° C.

Rationale of the Evaluation of the Alcohol Paravertebral Block. It is well established that if, after the interruption of the vasoconstrictor pathways to an extremity, that extremity is exposed to a cold environment, the skin temperature of the blocked limb tends to be higher than the unblocked limb; at least 2.5° C. higher.[2] The skin temperature of the unblocked limb, however, tends to approach the cool environmental temperature.

In our series we tried to determine how long this temperature difference was maintained, and, as mentioned before, as long as a significant difference in temperature existed in the two limbs at corresponding areas, vasodilatation as a result of the block was considered to be present.

Results. A. *Vasodilation.* Group 1 (6 cases). Two per cent novocaine, 5% novocaine in sweet almond oil; 1 cc. of 100% alcohol: One patient showed no effect, but 5 of the 6 patients showed an immediate vasodilatation; 2 for 3 days, 1 for 10 days, 1 for 2 weeks, and 1 till the present writing, 2 years.

Group II (4 cases). Two per cent novocaine, alcohol 1 cc.: Two cases showed no immediate effect, but 1 of these showed some vasodilatation 3 days later which was temporary. Two cases showed an immediate effect which lasted 10 and 24 days respectively.

Group III (6 cases). Two per cent novocaine with alcohol 3 cc.: Three cases showed no immediate result, but did show vasodilatation later; one 7 days later, another showed the first effect 14 days later and has continued till the present (11 months); the third showed a slight effect in 4 days and still continues to show vasodilatation at present (18 months). The other 3 cases showed an immediate full vasodilatation and lasted 10 days and from 109 to 182 days respectively. In other words, all patients in this series showed some effect, 2 showing an effect 11 and 18 months respectively. So that Group III patients gave the largest number of successful vasodilatations, but 1 case in Group I showed a remarkable result with only 1 cc. of alcohol.

Summarizing the total vasodilatation effect in 14 successful blocks, 5 cases showed complete immediate vasodilation lasting 3 to 108 days, 9 cases showed an immediate significant or delayed significant vasodilatation lasting 3 days to 2 years.

In our past studies we have noted the difficulty in producing complete peripheral vasodilatation at room temperature below 21° C. We thought it therefore advisable to check our cases and see if any immediate results had any relationship to the room temperature in which the block was done. In no case did the room temperature ever vary more than 2.2°, although in most cases it was fairly constant. The following are the results: The 5 cases showing complete immediate

vasodilatation were done at a room temperature of 19.6° to 26.4° C.; the 7 cases showing an incomplete but significant difference in temperature were done at room temperatures of 18.6° to 26.6° C.; those showing no immediate effect were done at room temperatures of 20.6° to 26.1° C. So that the room temperature at the time of doing the block was no factor in the vasodilatation effect.

B. *Neuritis.* Group 1 (6 cases). Two per cent novocaine, novocaine in oil, alcohol 1 cc.: Two patients had neuritis lasting 18 and 28 days respectively. One had pain in the gluteal region, and the other had pain in the gluteal region radiating to the inguinal region and the knee. One case had local pain for 10 days.

Group II (4 cases). Two per cent novocaine, alcohol 1 cc.: There were no instances of neuritis, but 2 patients had local pain lasting 3 and 4 days respectively.

Group III (6 cases). Two per cent novocaine, alcohol 3 cc.: Four cases had neuritis. One was not followed. The neuritis in the remaining 3 lasted 10 days, 14 days and 45 days respectively. The neuritis consisted of "electric shocks" in the anterior thigh, pain in the abdomen and thigh, and pain in the right testis.

Novocaine in sweet almond oil, therefore, had no effect in avoiding painful neuritis. It seemed also that the use of larger amounts of alcohol tended to produce neuritis more often, although in all cases followed, the neuritis was of relatively short duration.

C. *Claudication Time* (Graded 0 to 4+).[3] Claudication time was evaluated in 10 of the 12 cases of peripheral vascular disease, and the patients were followed for 12 to 24 months. Five showed improvement, 3 showed no change in claudication status, and 2 were definitely worse, complaining that pain set in earlier than it did before the block. Study of the relation between the claudication time and the result of the paravertebral block showed, that the 2 patients who had become worse after the block, had shown no vasodilatation at any time. However, there was no definite correlation between the improvement in claudication time and either the degree or the duration of the vasodilatation.

Comment. There are several points which deserve mention in consideration of alcohol paravertebral block.

I. *Technique.* It is seen that in many cases, while there is an immediate vasodilatation, this effect disappears after 3 or 4 days. White[8] has pointed out, that when novocaine is injected, it tends to diffuse through the tissues, and so reach the ganglia or sympathetic nerve fibers, even though the point of the needle is not directly in contact with the ganglia. Under these circumstances, when the alcohol is injected, it will not have the permanent destructive effect at the desired spot, and, although there is an immediate effect, the benefit is not lasting. One can only hope that, with skill and experience, the area sought for may be reached more often.

II. *Neuritis.* It may also be seen that novocaine in oil prior to the injection of alcohol does not prevent the occurrence of neuritis; that

neuritis occurs most often when larger amounts of alcohol are injected; and that neuritis, when it does occur, is not too severe, does not last very long, and should not be a deterrent to alcohol paravertebral block, when such a procedure is indicated.

III. *Claudication Time.* In a few patients (8) studied who showed vasodilatation, improvement or non-improvement of claudication time was not related to the degree or duration of the vasodilatation.

IV. *Degree and Duration of Vasodilatation.* Full vasodilatation as a result of paravertebral block occurred in 31% of the patients, immediately after injection of novocain. The injection of alcohol allowed this vasodilatation to be more lasting than if novocaine were used alone, but in no instance was the degree of vasodilatation as great after a few days had passed. However, 14 of the 16 patients showed vasodilatation effects lasting 3 days to 2 years. The amount of alcohol used was not the factor that determined how long this vasodilatation lasted, because the longest and best effect occurred in 1 patient who received only 1 cc. of alcohol (2 years). However, when 3 cc. of alcohol were used, there was uniform success in producing vasodilatations. Although the period of study covered only 2 years and showed that vasodilatation can last this long, there is reason to believe that the effects will last longer, and certainly long enough to produce beneficial results in the treatment of thrombo-angiitis obliterans and arteriosclerosis obliterans.

Conclusion. 1. The use of 100% alcohol in lumbar paravertebral block is of definite value in producing peripheral vasodilatation. This vasodilatation may be complete, and may last for varying periods of time, even up to 2 years and perhaps longer.

2. The neuritis that is produced as a result of such a procedure occurs more often when larger amounts of alcohol are injected; it is not too severe and in no instance has lasted more than 45 days.

3. The use of novocaine in sweet almond oil did not reduce the incidence of neuritis.

4. Vasodilatation occurred more often when larger amounts of alcohol were used, but the amount of alcohol was not the factor that determined how long this vasodilatation lasted.

5. There was no correlation between claudication time and the degree or duration of vasodilatation.

REFERENCES

1. Gootnick, A., Saland, G., Klein, C., and Zurrow, H.: J. Lab. and Clin. Med., **27**, 878, 1942.
2. Lewis, Sir Thomas: Vascular Disorders of the Limbs, New York, Macmillan, p. 16, 1936.
3. Saland, G., Klein, C., Zurrow, H., and Katz, A.: Arch. Int. Med., **65**, 1935, 1940.
4. Stern, E. L.: Am. J. Surg., **10**, 107, 1930.
5. Swetlow, G. I.: Am. Heart J., **1**, 393, 1926.
6. White, J. C.: The Anatomic Nervous System, New York, Macmillan, p. 371, 1935.
7. White, J. C.: The Anatomic Nervous System, New York, Macmillan, p. 375, 1935.
8. White, J. C.: The Anatomic Nervous System, New York, Macmillan, p. 369, 1935.
9. White, J. C.: Surg., Gynec. and Obst., **71**, 334, 1940.

AMEBIASIS: ANALYTICAL STUDY OF THE CASES ADMITTED TO A PHILADELPHIA HOSPITAL DURING THE LAST 5 DECADES

By R. S. Diaz–Rivera, M.D.

FELLOW IN INTERNAL MEDICINE OF THE SCHOOL OF TROPICAL MEDICINE, SAN JUAN, PUERTO RICO, AND LECTURER IN TROPICAL MEDICINE, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE

AND

Edwin A. Rasberry, M.D.

FELLOW IN GASTRO-ENTEROLOGY AND ASSISTANT INSTRUCTOR IN MEDICINE, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE
PHILADELPHIA, PA.

(From the Gastro-intestinal Section [Kinsey-Thomas Foundation] of the Medical Clinic, Hospital of the University of Pennsylvania)

Amebiasis is achieving a new importance during these unfortunate years of war, since at any time it may become a menace to both the civilian population and the armed forces. The old idea that amebiasis is essentially a tropical and subtropical disease is totally fallacious, and it has been thoroughly exploded by Craig[2] and Faust.[3] It is true that the disease is more common in the tropics, where in many regions an incidence of 50 to 90% is not a rarity, but it must be remembered that an estimated incidence of close to 20% has been reported for the United States as a whole.

An increase in the incidence of the disease in the United States after the war is predicted. Many of our soldiers are certain to be infested with the parasite in the tropical theaters of war. Some will become "cyst carriers" and, as such, though themselves free of symptoms, will lead to the development of the disease and its complications in the civilian population.

The diagnosis of this disease, though it can be accomplished by a relatively simple laboratory procedure, is not always easy. It depends on the demonstration in the feces of the parasite in its cystic or vegetative form. Unless the disease is suspected on the basis of an unexplained diarrhea or because of some complication, such a study often is not undertaken. Furthermore, unless a trained parasitologist is available, the organisms may not be recognized.

Goldburgh[4] in 1936 reported that among 232,100 admissions to the Philadelphia General Hospital from 1926 to 1935 only 1 was diagnosed as amebic dysentery. The admissions to the Jefferson Hospital during this same period amounted to 120,000, of which but 6 were diagnosed as amebic dysentery. These 6 cases were traced back to the Chicago epidemic in 1933. The same author reports that up to 1935 the Bureau of Health of Philadelphia had recorded only 43 cases of the condition, all of which occurred after 1933. In a careful survey to determine the incidence of protozoal infestation among patients admitted to the Hospital of the University of Pennsylvania during the winter of 1932–1933, Hinshaw and Showers[5] reported that probably 1.9% were suffering from amebiasis. In 1934 the stools of 1040 freshman stu-

dents from a professional school in Philadelphia were carefully examined, and 4.1% were reported as positive for *E. histolytica*. In 1937 Arnett[1] found among 293 fecal examinations on food handlers in a Philadelphia institution, that 6.5% were positive for the parasite. He also reported an incidence of 11.3% of infestation with *E. histolytica* among the inmates and employees of an institution for the aged in the same city. He concluded that 5 to 10% of the population in this area harbored the parasites. We were unable to find definite information as to the incidence of the disease in the whole state of Pennsylvania.

We are now presenting an analysis of the cases of diagnosed amebiasis in the Hospital of the University of Pennsylvania during the last 50 years.

Analysis of Data. During the last 5 decades, among approximately 61,574 admissions to the various medical services of the Hospital of the University of Pennsylvania, 32 cases were diagnosed as amebic dysentery, 4 of which were complicated with hepatic abscess. Of 4764 deaths among the medical admissions of this period, only 1 was regarded as due to amebic dysentery. Out of 122,933 surgical admissions with 5233 deaths, only 1 was due to amebic hepatic abscess.

Twenty-five of the records were complete and serve as the basis of this report; the rest, although they relate to cases of amebiasis by demonstration of the *E. histolytica* in the stools, have been discarded because insufficient data are available.

Sixteen of the patients acquired the disease prior to 1933, while 9 contracted it after that year. Twelve of those who contracted the disease prior to the Chicago epidemic had been in a foreign country when they noticed their first symptoms. Thus, there were only 4 cases prior to 1933 that were infected in the United States, and of these, 1 had been in Chicago in 1924 where he was taken ill with diarrhea, while 1 had acquired the disease in New York City and 1 in Georgia. Of the 9 cases admitted after 1933, 2 acquired the infestation during the Chicago World's Fair, and one in Poland. Thus, at most only 7, 1 before and 6 after 1933, apparently acquired the disease in Pennsylvania or nearby, and 5 of these were admitted during the last 6 months.

Residence in an infested area was obviously a great aid in the diagnosis of the earlier cases, while native Pennsylvanians were not often suspected. Thus, more than half (13) of the 25 cases had been in a foreign country, either the Philippines, Hawaii, Greece, Italy, Russia, Rumania, Poland, England, France, Costa Rica, Brazil, China or Mexico; the 5 diagnosed during the last 6 months, however, have not traveled outside the state of Pennsylvania.

The ages of the patients varied from 11 to 60 years. Fourteen were between 21 and 40 years old and 6 were 40 years or older, while 5 were in the first two decades of life. Twenty-two were males; 3, females, thus giving a sex ratio of 7 to 1. Twenty-two were white and 3 colored. All 4 of those with an hepatic abscess were males, 2 of whom were colored.

The patients had various occupations, being students, laborers, food handlers, soldiers, sailors, librarians, accountants or lawyers, and one was a gypsy.

Eleven gave a definite history of seasonal onset. Four had the initial symptoms during the fall, 2 during the spring, 3 during the summer and 2 during the winter. The onset was acute in 14 and insidious in 11. Sixteen were admitted during the winter, 5 during the summer, and 4 during the fall. The duration of the disease before hospitalization varied from 3 months to 17 years (average, 4.3 years). Only 7 patients were admitted within the first year of the onset of their symptoms.

Symptomatology and Physical Observations. As shown in Table 1 the most prominent symptom in the patients studied was diarrhea, 24 of the patients having at some time a severe diarrhea with 4 to 20 movements daily. In all of these, remissions and exacerbations were the rule. The remaining symptoms most commonly complained of were: blood in the stools, mucus in the stools, abdominal pain, rectal tenesmus, dyspepsia, fever, loss in weight, headache, chills and jaundice. The most important physical finding was abdominal tenderness, observed in 19 of the cases. Hepatomegaly was recorded in 8 cases and it was due to hepatic abscess in 3 of these. Mild jaundice was observed in 2 of the 4 patients suffering from hepatic abscess.

TABLE 1.—SYMPTOMS AND SIGNS OF 25 CASES OF AMEBIASIS

	No. of cases	%
Diarrhea	24	96
Remissions and exacerbations	24	96
Bloody stools	21	84
Pain in abdomen	20	80
Mucus in stools	19	76
Abdominal tenderness	19	76
Tenesmus	17	68
Fever	17	68
Loss of weight	17	68
Hepatomegaly	8	32
Nausea and vomiting	7	28
Anorexia	7	28
Headache	5	20
Chills	4	16
Jaundice	2	8
Constipation	1	4
Total	214	

Laboratory Observations. In 22 cases vegetative forms of *E. histolytica* were found in the feces; in 2, the cystic forms. In 1, motile amebæ were found in the pus draining from an hepatic abscess. In all of the most recent cases the diagnosis was confirmed by repetition of the stool examinations. Among 14 cases submitted to proctoscopic examination, 10 had ulcerative rectosigmoiditis; 2 presented catarrhal inflammation and in 2 the mucosa was normal. Eleven patients showed anemia. Anemia was severe in a patient with thrombocytopenic purpura hemorrhagica who had become infested with *E. histolytica* some 3 years previous to admission. Eleven cases had a leuko-

cytosis. Eosinophilia was encountered in 9 instances, ranging from 9 to 12%. No other ova or parasites were seen in the feces in any case.

Treatment. The treatment consisted of colonic irrigations of plain water at a temperature of 43° to 45° C. in 6 of the cases. Warm irrigations of mercurochrome, quinine and silver salts were given to 3 patients. Kerosene irrigations were prescribed in 1 instance. Emetine hydrochloride was used in conjunction with other amebecidal drugs, including carbarsone, stovarsol and chiniofon in 16 cases. Surgical drainage and emetine hydrochloride were employed in the treatment of the 4 cases suffering from hepatic abscess. In the majority of the patients the treatment was inadequate by present standards.

Two patients died (8%), both from complications; hepatic abscess in one and perforation of the bowel in the other. Autopsy was not permitted. Twenty-two of the patients were discharged as improved, and 1 is at present under observation but recovering rapidly. Due to lack of proper follow-up the true percentage of cures cannot be reported with accuracy, especially in the cases admitted previous to 1933. Below we present abstracts of case histories of 3 patients, 1 showing a typical abscess, 1 with an unusual type of abscess and 1 of the patients who died.

Case Studies. CASE 1. E.B., a 32 year old negro, was admitted to this hospital on January 20, 1938. He had been well until 9 days previously when he developed pain in the epigastric and presternal regions which was intensified by deep breathing. He had had frequent bouts of diarrhea after traveling in South America in the years 1930–1932. He was hospitalized in the Boston City Hospital in 1935 because of bloody stools and right upper quadrant pain, with diagnosis of chronic cholecystitis and toxic hepatitis. A cholecystotomy was performed at that time.

On this admission examination revealed a temperature of 102.5° F., pulse of 114 and blood pressure of 118 systolic and 82 diastolic. He was slightly jaundiced and breathing was rapid and shallow. He complained of severe stabbing pain in the right upper quadrant and over the hepatic area there was exquisite tenderness. There was definite diaphragmatic lag on the right side. His leukocyte count was 21,200, with a normal differential; the red blood cells numbered 3.54 millions, with a hemoglobin of 68%. The van den Bergh test was immediate direct and the indirect reading was 4 units. Urine was positive for bilirubin and bile salts. The Kolmer and Kahn tests were weakly positive. The stool examination was positive for *E. histolytica* trophozoites 2 days after admission.

Three days after admission surgical exploration revealed an abscess the size of a hen's egg close to the diaphragm in the mid-zone of the liver anteriorly. Treatment consisted of drainge and emetine hydrochloride subcutaneously. He was discharged cured.

CASE 2. C.J., a 46 year old negro, admitted to the Hospital of the University of Pennsylvania on November 25, 1941, was well until 18 months previous to admission when he developed a bloody diarrhea and tenesmus. Two weeks before admission he started to complain of headache, chills, fever, dizziness and pain in the right upper quadrant. He had been in foreign countries while in the Army and Navy, but for the past 5 years had been a resident of Philadelphia.

On examination his temperature was 101° F., pulse 100, and respiration 24. Dullness, increased tactile fremitus and fine râles were encountered at the base of the right lung. There was marked tenderness and rigidity in the right upper quadrant. His leukocyte count was 21,000 and the hemoglobin was 65%. A chest plate demonstrated increased bronchial markings suggestive of bronchiectasis.

The day following admission an exploratory laparotomy was done and an acute catarrhal inflammation of the gall bladder was encountered. A cholecystotomy was performed. The draining bile appeared normal, and drainage continued for a few days. This gradually faded in color and decreased in amount; about the 10th postoperative day he began to drain frank pus. The right upper quadrant pain recurred, the liver became markedly enlarged and on the 24th postoperative day drainage became profuse and reddish in color. Two days later the incision was enlarged and an enormous liver abscess was drained. This had perforated spontaneously into the gall-bladder and had partially drained through the tube left *in situ* at the first surgical intervention. Examination of the pus revealed motile *E. histolytica* trophozoites. Following emetine hydrochloride the parasites were eradicated from the draining pus and they were not at any time found in the feces. He was discharged 2 months after admission, but the patient was subsequently readmitted to the hospital for a recurrence of the diarrhea, blood in stool, and tenesmus. Intensive treatment with emetine, chiniofon, and carbarsone, however, rendered the feces free of amebæ and the patient was discharged as cured.

Case 3. C.S., a 14 year old white female, was admitted to this hospital on November 16, 1922, complaining of intermittent attacks of bloody diarrhea for 3 years. Two years previously she was told that she had amebic dysentery and was treated with emetine for 3 weeks. Subsequently she received emetine and ipecac sporadically, but during the 9 months previous to her admission such medication was of no avail.

Examination showed that she was cachectic. Red blood cells numbered 3.9 millions, with a hemoglobin of 65%. Her leukocyte count was 16,200 with an eosinophilia of 10%. The stools were grossly bloody and motile forms of *E. histolytica* were seen. Proctoscopic examination revealed diffuse ulceration of the mucosa of the rectum and sigmoid.

The patient's course was steadily downhill. She had as many as 20 bowel movements a day terminally. She developed a low-grade fever, and in spite of colonic irrigations, emetine hydrochloride, kaolin, paregoric, bismuth subcarbonate, transfusions and general supportive measures, she died 30 days after admission.

Comment. It has been demonstrated that amebiasis is a serious problem in any locality, and that the city of Philadelphia is no exception. Nevertheless, during the past 5 decades only 32 cases of this disease have been diagnosed and treated in this hospital. Thus, only about 0.05% of all medical admissions were cases of amebiasis. This, undoubtedly, is a small percentage when one considers that the incidence of infestation in special groups in the city has been shown to be approximately 5 to 10%. Furthermore, only 7 cases were known to have acquired the disease in Philadelphia or nearby, perhaps indicating that the index of suspicion in this region is low. Undoubtedly, the tendency has been to make stool examinations in those patients who traveled in the tropics because amebiasis abounds there. We believe that many cases were probably missed because not enough stools were examined. A stool examination is not a routine procedure in many hospitals in the United States, but at least in all cases of diarrhea such studies should be required.

There was only one patient listed in our files who could be classified as asymptomatic at the time of admission. Nevertheless, he gave a history of traveling in South America, and besides stated that he had had relapses and exacerbations of bloody diarrhea. Of the 32 cases admitted to this hospital during the last 50 years, 5 were diagnosed

and treated during the last 6 months. It seems likely that intensified interest in the disease has been responsible for the increase in the number of cases diagnosed recently.

Evaluation in the treatment of amebiasis is apparent in this series of cases. In the last few years treatment standards have improved considerably. Present-day medical therapy consisting of intensive courses of emetine, chiniofon and carbarsone has been shown to be more effective than former therapeutic regimens, and liver abscesses are better managed by simple aspiration and emetine rather than by the now obselete, open operation.

Conclusion. An increase in the incidence of amebiasis is to be expected in the United States after the war, as the disease, no doubt, will be brought into this country by service men returning from the tropics. Epidemics may arise from chronic "cyst carriers."

Although the incidence of the disease in Philadelphia has been estimated to be 5 to 10%, only 32 cases have been diagnosed at the Hospital of the University of Pennsylvania during the last 5 decades. Five of these cases have been diagnosed during the last 6 months. Until recently, interest in amebiasis in this locality has been at low ebb.

Complications of the disease are not uncommon, as evidenced in this series of 25 cases. A high index of suspicion and a competent parasitologist to do stool examinations are necessary prerequisites for proper diagnosis.

We are indebted to Dr. T. Grier Miller for his assistance in the preparation of this report.

REFERENCES

1. Arnett, J. H.: Rev. Gastroint., **6**, 91, 1939.
2. Craig, C. F.: Amebiasis and Amebic Dysentery, Springfield, Ill., Charles C Thomas, 1934.
3. Faust, E. C.: Am. J. Trop. Med., **22**, 93, 1942.
4. Goldburgh, H. L.: Ann. Int. Med., **10**, 926, 1936.
5. Hinshaw, H. C., and Showers, E. M.: Am. J. Med. Sci., **188**, 108, 1934.
6. Ochsner, A., and De Bakey, M.: New Internat. Clin., **1**, 68, 1942.
7. Wenrich, D. H., Stabler, R. M., and Arnett, J. H.: Science, **79**, 143, 1934.

TRICHINELLA SKIN TESTS IN PATIENTS IN GENERAL HOSPITALS AND TUBERCULOSIS SANATORIA*

By S. F. Horne, M.D.
ASSISTANT RESIDENT IN MEDICINE
AND
George T. Harrell, M.D.
ASSISTANT PROFESSOR OF MEDICINE; ASSOCIATE PROFESSOR OF PREVENTIVE MEDICINE
WINSTON-SALEM, N. C.

(From the Departments of Medicine and Preventive Medicine, Bowman Gray School of Medicine)

The study of routine autopsies has revealed a great variation in the incidence of trichinella infestation in different parts of the United

* The trichinella antigen and control solutions in this study were supplied by Lederle Laboratories, Pearl River, N. Y.

States. In Rochester, N. Y., the incidence was reported to be 17.2%, in Boston 27.6%, in San Francisco 24%, in Minneapolis 17.1%, in New Orleans 3.5% and in St. Louis 15.5%.[5] In a study of 105 autopsies in North Carolina, 3 (2.8%) instances of trichinosis were found. The diaphragms from these patients were examined by both the muscle press and digestion technique.[5] The present study was undertaken to compare the percentage of cases found to have evidence of infestation as determined by positive intradermal reactions with the previously determined incidence at postmortem examination.

Kaljus[6] points out that Fülleborn first proposed the idea of a skin test for the diagnosis of trichinosis, but he was unable to isolate the parasites in the pure state. A few years later Bachman developed a method for obtaining isolated trichinæ and, by a process of drying and extracting, obtained an antigen which gave a positive skin test in infected rabbits and guinea pigs.[6] An antigen prepared by the Bachman technique was first used in man by Augustine and Teiler.[6]

In 1937, Spink[9] noted that two types of reaction occur in humans: an immediate reaction with blanched wheal, occasional pseudopods and (reticulated) erythema which appears within 5 minutes, and a delayed reaction with (solid) erythema and edema which does not become positive for 12 or more hours and is read 24 hours after the test is given. The immediate reaction is not obtained until the 2d week of infection, usually on or after the 17th day. The delayed response is elicited only early in the disease.

Since that time numerous reports have appeared of the use of the intradermal reaction in the diagnosis of trichinosis. McCoy, Miller and Friedlander[7] used 1:10,000 and 1:500 dilutions of antigen. In early known infections of 6 weeks or less, immediate reactions were obtained in 70% with the 1:10,000 dilution; in late infections of 3 to 22 months duration 49%, and in infections of 3 to 7 years duration 23% were positive. A control series showed 9% positive reactions in Rochester and 4% in San Francisco in individuals tested at random; 18% of patients in Louisiana infected with *Trichuris trichura* gave positive tests. Schapiro, Crosby and Sickler[8] found an incidence of 18.3% in 400 unselected individuals in Washington, D. C. Gould[2] found 5.9% positive reactions in 2940 patients in Detroit.

Recently, several studies have been made which correlate the incidence of trichinosis found at autopsy with that found by routine skin test. Schapiro *et al.*[8] reported 116 patients who were skin-tested during life and examined for trichinella larvæ at postmortem. Larvæ were found in 26 of the patients of whom 24 had given positive immediate reactions (92.3%); the other 2 patients had light long-standing infections. No larvæ were found in 90 of whom 3 had given (false positive ?) immediate reactions (3.3%). Gould[2] examined 388 patients at autopsy for trichinella larvæ, all of whom had been skin-tested during life. Using a 1:10,000 antigen, he found that only 10.1% of the patients who were found to have trichinella larvæ at autopsy had given a positive immediate intradermal reaction and in those in whom no trichinæ were found immediate (false positive ?) reactions were

obtained in 5.4%. The failure of correlation of clinical and autopsy findings was attributed to mild, long-standing subclinical infections.

In view of the great variation in the incidence found at autopsy and by skin test, it is desirable to determine the prevalence by a more sensitive method than the examination of diaphragms. When the digestion method is used, the live larvæ are found, but the dead ones are disintegrated and, consequently, missed. The muscle press method is of value only in moderate or heavy infections, although it does find both living and dead larvæ. The skin test should not have these limitations, since it may be positive regardless of whether the infestation is light or heavy, or the larvæ dead or alive.

Material. A total of 700 patients were skin-tested; 278 consecutive admissions to the North Carolina Baptist Hospital, 144 patients at the Forsyth County Hospital, 120 patients at the Guilford County Tuberculosis Sanatorium, and 158 patients at the Western North Carolina Tuberculosis Sanatorium. Of the patients, 522 were white and 178 negroes; 315 were males and 385 females. The youngest patient was 9 years of age, the oldest 111. In 558 of the patients, the presence or absence of a history of an allergic condition was noted. Seventeen individuals gave a history of allergy; 9 had attacks of asthma, 2 of allergic dermatitis, 2 of urticaria, 2 of hay fever, 1 of hay fever and asthma, and 1 patient had asthma, hay fever, migraine, and allergic dermatitis.

Method. In all instances a 1:10,000 trichinella extract and a saline control solution were used. An area on the flexor surfaces of both forearms was cleaned with alcohol and 0.02 to 0.03 cc. of the test and control solutions were given intradermally in separate arms. The reactions were read 15 to 20 minutes and 24 hours later; the degree of erythema and wheal and the presence or absence of pseudopods were noted. The reaction was recorded as positive when the diameter of the area of erythema with induration exceeded that of the injected bleb by 5 mm., or when the wheal exceeded the diameter of the injected bleb by 3 mm. If the control injection produced a reaction, the test was recorded as negative.

New syringes and needles were obtained for the skin tests and were not used for any other purpose. One syringe and needle was always used for the test solution and another for the control; the syringes and needles were never interchanged. After being used they were washed with distilled water, placed in glass tubes, and sterilized in an autoclave.

Results. Seventy of the 700 patients (10%) gave positive tests. The incidence at the Baptist Hospital was 5.8%, at the Forsyth County Hospital 10.4%, at the Guilford County Tuberculosis Sanatorium 16.9%, and at the Western North Carolina Tuberculosis Sanatorium 13.3%. Of the 70 positive tests, 68 were immediate reactions; in 10 patients the positive reaction persisted for 24 hours. In 2 patients the reaction was delayed in type. The incidence among the white patients was 9.1%; among the negroes 11.8%. The patients who had spent most of their lives in a community with a population of 2500 or less were classified as rural inhabitants and showed 9.8% positive reactions; those living in larger communities, the urban group, showed 10.3% positive reactions. The incidence in males was 11.1%, and in females 8.8%. Tuberculosis was present in 283 patients and 14.3% gave positive reactions; the incidence in those without known or clinical tuberculosis was 7.1%. Among the patients

with tuberculosis 17.2% were negroes; 30% of those without tuberculosis were negroes. Table 1 summarizes the findings.

TABLE 1.—RESULTS OF 700 SKIN TESTS WITH TRICHINELLA ANTIGEN 1:10,000

	Patients tested	Patients positive	% positive	chi square	p	Interpretation
White	521	48	8.0	1.4044	>.20<.30	Not signif.
Negro	179	22	12.3			
Male	315	36	11.1	..	..	Not signif.
Female	385	34	8.8			
Rural	400	39	9.8	..	..	Not signif.
Urban	300	31	10.3			
Tuberculous	283	40	14.3	9.022	<.01	Highly signif.
Non-tuberculous	417	30	7.1			
White:						
Tuberculous	235	32	13.6	9.6845	<.01	Highly signif.
Non-tuberculous	286	16	5.6			
Negro:						
Tuberculous	48	8	16.7	1.1524	>.20<.30	Not signif.
Non-tuberculous	131	14	10.7			
Total	700	70	10.0			

Five (29.4%) of the allergic patients were positive to both the test and control solutions and were counted as negative; 10 (58.8%) had a negative test and control, hence only 2 (11.8%) were considered to have a positive reaction. One patient had a typical strongly positive test while acutely ill with asthma and dermatitis, and again when retested after recovery from the attack.

One patient with recognized hookworm infestation gave a positive test; repeated tests were positive 1 week and 6 weeks after anthelmintic therapy. One and 6 weeks after treatment, which resulted in the passage of parasites, stool examinations were negative for ova and parasites. Stool examinations were not done on all patients; this one instance was thought to be a coincidental infestation.

None of the patients with positive reactions gave a history which suggested acute trichinosis, although the majority consumed fairly large amounts of pork which may not always have been well cooked.

No untoward systemic or local reactions to the test were observed.

Discussion. The incidence of infestation as determined by intradermal test (10%) is definitely higher than that previously found here at autopsy (2.8%).[5] In the study of autopsies only a small portion of the total musculature is examined. The skin test should determine sensitivity to the parasites regardless of where they have localized or in what concentration. The difference in incidence reflects the relative effectiveness of the two methods in discovering past infestation. Lack of specificity of the intradermal reaction, which might account for a higher incidence by this method, has not been demonstrated when a dilution of 1:10,000 is used.[6]

The incidence in other parts of the country is greater than that

found here, as determined by the study of autopsy material. By skin test by the same technique, the findings have varied widely. The incidence of trichinosis in grain-fed hogs is 1 to 1.5% and 4.8% in those fed garbage.[4] The majority of hogs in this section are grain-fed. Uncooked or prepared pork products such as blood sausage and salami are not eaten in the South as much as in the North where the incidence of the disease is higher.

The incidence was 9.8% among rural inhabitants and 10.3% among residents of towns with a population of 2500 or more. This does not support the contention that trichinosis is principally a disease of rural areas. The source of pork in North Carolina is essentially the same in rural and urban areas; the majority comes from small, local packing houses, though in the large cities western meat processed by large packers is sold.

More reactions were found in males than in females: 11.1% and 8.8% respectively. Men are more likely than women to eat away from home at roadside cafes where cooking is unreliable, and where pork products, such as barbecue and sausage are featured. Women may develop the disease while tasting sausage and other similar raw or partially cooked pork products while these foods are being prepared.

The apparent increase in incidence among negroes, 12.3% against 8% in the white patients, would not be surprising, if true, since the negro tends to prepare food poorly. However, the difference is not statistically significant.*

TABLE 2.—INCIDENCE OF POSITIVE REACTIONS TO TRICHINELLA ANTIGEN IN 700 PATIENTS ACCORDING TO AGE

Age group	Patients tested	Patients positive	% positive
0– 9	1	0	0
10– 19	43	5	11.6
20– 29	198	21	10.6
30– 39	163	15	9.2
40– 49	120	9	7.5
50– 59	75	11	14.7
60– 69	47	4	8.5
70– 79	36	3	8.3
80– 89	16	1	6.3
90– 99			
100–109			
110–119	1	1	100.0
Total	700	70	10.0

Hall,[3] studying the ages of the 1000 persons whose diaphragms were examined by Nolan and Bozicevich, found an incidence of 16% in persons up to 50 years of age, and 19.5% in those over 50. In the study of muscle removed at autopsy, Gould[2] also found a greater incidence with increasing age which he attributed to the greater number of opportunities for exposure to trichinæ as the individual grows older. Using the intradermal test he found a slight decrease in incidence with advancing age. In the present series 524 individuals were under

* We are indebted to Dr. Donald S. Martin, Duke University School of Medicine, Durham, N. C., for statistical criticism of our results.

50 years of age, of whom 50 (9.5%) gave positive reactions; 176 were over 50 years of age, and 20 (11.4%) gave positive reactions. No gradual increase in incidence with advancing age was noted (see Table 2); the difference in incidence among the patients under and over 50 is of doubtful significance. Some individuals over 50 years of age, who had trichinosis when young, might have lost their sensitivity and hence ability to give a positive skin reaction. It has been reported that in some instances the skin test remained positive for 7 years after infection, while in others a negative test was found 4 years after the illness.[7]

Arbesman, Witebsky and Osgood[1] have found that allergic individuals show a higher incidence of positive reactions than do non-allergic subjects. Others believe that the allergic state predisposes to false positive non-specific reactions.[7] This was not the finding of Gould.[2] The incidence among 17 white allergic patients of the present series was 11.8%. This is higher than the incidence found among the entire group of white patients (8%), but since the number is small, is probably of no significance. Allergic individuals have an hyperactive skin, which one would expect to react to the control as readily as to the test solution; 5 of our allergic patients reacted to both, hence were considered negative in the statistical analysis.

The rise in incidence among patients with tuberculosis is striking (Table 1) and, so far as we have been able to determine, has not been previously reported. The difference is statistically significant. The increase in positive reactions was noted in both negroes and whites with tuberculosis. Although the incidence is higher in all negroes than in whites, the number of whites with tuberculosis was far greater than of negroes, hence this factor was not significant. Since the syringes and needles used in this study were never used for any other purpose, and were never sterilized by boiling, no chance contamination with tuberculin occurred. The larvæ from which the antigen was prepared were recovered from rabbits which had never received injections of tuberculin, nor was tuberculin ever used or made in the laboratory where the antigen was manufactured.

Almost all of the patients with tuberculosis were in 2 sanatoria; it is possible that these findings represent the result of 2 local, unrecognized or subclinical epidemics. In 1 sanatorium the hogs were garbage-fed and reared on the grounds; in the other the pork was purchased, for the most part, from large packers. In any institution where the quantity used is greater than in a private home, pork is frequently less thoroughly cooked. The size of the uncut portions cooked is larger and the center may be inadequately cooked even though the surface is thoroughly done. Of the 144 patients at the Forsyth County Hospital, 87 were confined to the chronic or mental wards and had resided in an institution for a period of time comparable to the stay of patients in a sanatorium. Of these, only 7 (8%) gave positive tests, suggesting that confinement or residence in an institution is not the sole explanation for the rise in the tuberculous group. The remainder of the patients at the Forsyth County Hospital and those

at the Baptist Hospital constitute the group in general hospitals where the stay in an institution is too short to be significant.

Other possible explanations are that patients with tuberculosis develop skin sensitivity with much lighter infestations or retain sensitivity longer than do non-tuberculous individuals, or that their skin is more reactive to intradermal tests in general. Personal communications from men with experience in treating tuberculosis indicate that, in general, they have not found their patients more reactive to intradermal tests than non-tuberculous individuals. It seems unlikely that these patients would develop a response to trichinella antigen and not to other materials commonly used for intradermal tests, for many patients had been used previously for passive transfer tests in the study of allergic conditions without evidence of unusual reactivity.

Summary. 1. The incidence of positive intradermal reactions to commercial trichinella antigen in North Carolina, was 10% in a series of 700 hospitalized patients. This is lower than similar studies have shown in some other areas of the United States.

2. The incidence found by skin test was greater than that found in routine autopsies in this geographic area.

3. The incidence was greater among negroes and in males, but was not statistically significant in either.

4. The incidence of positive tests was essentially the same in urban and rural groups.

5. Patients with active tuberculosis in 2 sanatoria gave a higher percentage of positive reactions (14.3%) than did those without tuberculosis (7.1%) in 2 general hospitals. This was found to be statistically significant.

REFERENCES

1. Arbesman, C. E., Witebsky, E., and Osgood, H.: J. Allergy, **13**, 583, 1942.
2. Gould, S. E.: Am. J. Hyg., **37**, 1, 1943.
3. Hall, M. C.: Pub. Health Rep., **53**, 1086, 1938.
4. Hall, M. C.: Pub. Health Rep., **52**, 873, 1937.
5. Harrell, G. T., and Johnston, C.: South. Med. J., **32**, 1091, 1939.
6. Kaljus, W. A.: Puerto Rico J. Pub. Health and Trop. Med., **11**, 768, 1936.
7. McCoy, O. R., Miller, J. J., Jr., and Friedlander, R. D.: J. Immunol., **24**, 1, 1933.
8. Schapiro, M. M., Crosby, B. L., and Sickler, M. M.: J. Lab. and Clin. Med., **23**, 681, 1938.
9. Spink, W. W.: New England J. Med., **216**, 5, 1937.

HEART BLOCK

A Study of 100 Cases With Prolonged P–R Interval

By Robert Bruce Logue, Major, M.C., A.U.S.
CHIEF OF CARDIOVASCULAR SECTION
AND
James Fletcher Hanson, Major, M.C., A.U.S.
ATLANTA, GA.

(From the Cardiovascular Section, Medical Service, Lawson General Hospital)

In a study of 6732 electrocardiograms taken on 4264 patients at the Lawson General Hospital, there were 100 instances of first degree heart

block, with P–R intervals of 0.22 second or above. There were 12 additional instances with P–R intervals of 0.21 second which were omitted from this study since certain authors[4] feel that a P–R interval of 0.21 second is normal.

This study includes individuals observed in the Cardiovascular Section from July, 1941 to August, 1943. It represents patients treated in the Cardiology Wards as well as those observed in other sections and departments of the hospital on whom electrocardiograms and consultations were requested. Ninety per cent of the total number of patients observed had no symptoms or clinical evidence of heart disease and were seen because of routine requirements. The remaining 10% had evidence of heart disease. Of the 100 cases selected for this study, 91 cases had a complete cardiovascular survey, including Roentgen ray studies of the heart and lungs. The remaining 9 cases did not have cardiac consultations but did have electrocardiograms and complete physical examinations as well as Roentgen ray studies of the heart and lungs.

Etiologic Classification of Cases. In the 2-year period over which our observations extended, the incidence of heart block was 2.3% in the 4264 patients studied. The etiologic classification of the 100 cases is given in Table 1.

TABLE 1.—ASSOCIATED DISEASES IN 100 CASES OF FIRST DEGREE HEART BLOCK

1. Rheumatoid arthritis	5
2. Arteriosclerosis, coronary	12
3. Arteriosclerosis, generalized	2
4. Digitalis	2
5. Gonorrhea	8
6. Hypertension	1
7. Infectious diseases	5
8. Miscellaneous	11
9. Neurocirculatory asthenia	7
10. No disease found	19
11. Rheumatic fever	28
Total	100

In the arthritic group, there were 5 cases of rheumatoid arthritis. These findings are of interest because of recent investigations[1] in which rheumatic-like lesions have been found in hearts of people at autopsy who suffered with rheumatoid arthritis.

Of the 12 cases of coronary arteriosclerosis, 8 cases had myocardial infarction and 4 cases had angina pectoris.

Of the 2 cases in which generalized arteriosclerosis was the only causative factor of block, no other evidence of disease of the cardiovascular system could be determined.

There were 2 cases in which digitalis therapy was considered to be the cause of the prolonged P–R interval.

There were 8 cases of heart block found among 530 cases of sulfonamide-resistant gonorrhea, examined prior to the administration of fever therapy. All of these patients had received 2 or more courses of some sulfonamide drug 2 to 3 weeks before cardiac consultation. This represents an incidence of 1.5%. The cause of the heart block in this

group is not clear. It is felt that the block was not due to the sulfonamide drugs. The incidence of block in these cases compares favorably with the reported incidence of 1.5% of block[3] in a study of 1812 normal males who had P–R intervals above 0.20 and who had not received any type of drug therapy.

There was 1 case of hypertension; the blood pressure was 180 systolic and 100 diastolic.

In the group with infectious diseases, there was 1 case each of malaria, German measles and infectious mononucleosis. One patient had a history of scarlet fever and another a history of diphtheria during childhood. During the acute illness, the patient with German measles developed paroxysmal, complete heart block for a period of 24 hours. There was a subsequent return to normal of the P–R interval over a period of 1 week.

The miscellaneous group included such causative factors as spontaneous pneumothorax, mediastinal lymphoblastoma, congenital heart disease, acute and chronic nephritis, migraine, psychosis and tuberculous pericarditis. One patient had a past history of thyroidectomy in 1932 and another a history of syphilis in 1923.

There were 7 cases of neurocirculatory asthenia in which no evidence of organic heart disease could be determined.

Under the classification of no disease found, 19 patients were studied in whom, except for the prolonged P–R interval, no other evidence of disease of the cardiovascular system could be demonstrated. This group consisted of the following: 6 civilians who were candidates for commission, 2 instances of psychoneurosis, 2 of fractures and 1 instance each of psychosis, involutional melancholia, pylorospasm, obesity, upper respiratory infection, inguinal hernia, duodenal ulcer, traumatic hematemesis and 1 patient who was hospitalized for determination of physical fitness. There was no history or evidence of any disease that might reasonably be expected to be associated with a prolonged conduction time.

In the rheumatic fever group, there were 22 cases of acute rheumatic fever and 6 cases of chronic rheumatic infection. Of the entire group, 9 cases had chronic valvular heart disease, one of which gave no history of previous rheumatic infection. Four patients had acute pericarditis.

Of the entire series of 100 cases with block, 34% fell into the category in which no plausible explanation could be found for the prolongation of the P–R interval. This group was composed of the 19 cases in which no disease was found, the 7 cases of neurocirculatory asthenia and the 8 cases of gonorrhea.

Comment. The P–R intervals of the 100 cases are tabulated in Table 2. In 79 cases, the interval varied from 0.22 to 0.24 second; in 21 cases, the interval varied from 0.26 to 0.44 second. The variations in age and pulse rate are grouped according to the etiologic classification of the block.

In our series, the greatest incidence of block was in the 28 cases in which rheumatic fever was the causative factor. The next largest

incidences, in the order of their occurrence were as follows: the 19 cases in which no disease was found, the 12 cases with arteriosclerosis of the coronary arteries, the 11 cases in the miscellaneous group, the 8 cases in the gonorrhea group, the 7 cases in the neurocirculatory asthenia group, the 5 cases each in the arthritic and infectious disease groups, the 2 cases in the generalized arteriosclerotic group and the 1 case in the hypertensive group.

TABLE 2.—AGE, RATE, P–R INTERVAL and ATROPINE RESPONSE OF 100 CASES FIRST DEGREE HEART BLOCK

			P–R interval										Atropine	
Disease	Age	Rate	.22	.23	.24	.26	.28	.32	.34	.36	.40	.44	Pos.	Neg.
1. Arthritis	26–29	68–115	2		2	1							2	
2. Arteriosclerosis, coronary	24–60	60–110	5		5	1					1			
3. Arteriosclerosis, generalized	44–45	88– 90	1		1								1	
4. Digitalis	47–56	70– 90			2									
5. Gonorrhea	21–29	70– 83	3		2		3						4	1
6. Hypertension	30	100					1							
7. Infectious diseases	22–27	60–100	1		2		1			1			2	
8. Miscellaneous	18–53	60–120	3		7						1		1	1
9. Neurocirculatory asthenia	22–38	60–120	2		4		1						3	1
10. No disease	21–55	60–100	7	2	8	1					1		5	4
11. Rheumatic fever	19–49	50–120	10		10	1	2	3	1			1	7	6
Total			34	2	43	4	8	3	1	1	3	1	25	13

The high incidence of block in the group of cases in which no disease was found is of interest. Textbooks of medicine generally give 0.20 to 0.21 second as the upper limits of normal for auriculo-ventricular conduction time. Figures in excess of these are said to be abnormal and to suggest a pathologic cause. The incidence of block in this group suggests that a prolonged P–R interval may at times be found in a person in whom no apparent cause of the prolongation can be determined. White [10] states that it is probable that many individuals with P–R intervals of 0.21 or even 0.22 second have normal hearts. While it is impossible to eliminate past subclinical rheumatic infection as a causative factor in this type of case, it is our belief that an occasional person may have a prolonged conduction time which is normal for that person and is perhaps associated with an individual variation of vagal tone. The significance of vagal effect is not clear. Pardee[7] feels that it is extremely doubtful that overactivity of the vagus ever causes more than a transient accentuation of a condition fundamentally due to disease. Lewis[5] states, "It is questionable that persistent block in the human subject is ever attributable to inhibition. Unquestionably, persistent block of a high grade is not vagal in most patients who display it, for it is unaffected by full doses of atropine." On another occasion, the same author[6] states, "Minor grades are often brought about by vagal influence, that is by pressure on the carotid sinus; vagal block is usually temporary and is relieved by atropine." Poel[8] reported a case of incomplete auriculo-ventricular block due to vagal effect and commented on 2 previous reports in similar cases which responded to atropine. Weiss and Ferris[9] reported 2 cases of Adams-Stokes syndrome with transient complete block of vagovagal origin, associated

with the act of swallowing. In both cases, the block was relieved by atropine.

To study the effect of atropine on conduction time, doses of 1/75 grain were given intravenously in 38 cases of this series. In 25 cases, the P–R interval returned to normal, while in 13 cases, there was no change. Of the 38 cases in which atropine was used, 25 cases (65%) showed a return to a normal conduction time of 0.20 second or below. Those responding included 7 cases of rheumatic fever, 4 cases of gonorrhea, 5 cases in which no disease was found, 3 cases of neurocirculatory asthenia, 2 cases of sore throat, 2 cases of rheumatoid arthritis, 1 case of acute nephritis and 1 case of generalized arteriosclerosis. Of those not responding, there were 6 cases with rheumatic fever, 4 cases in which no disease was found, and 1 case each of neurocirculatory asthenia, gonorrhea and congenital heart disease.

We feel that the return to a normal conduction time, following the administration of atropine, indicates the block to be of vagal origin. However, the disappearance of auriculo-ventricular heart block after the use of atropine, does not mean that there may not be a pathologic change in the heart muscle or conduction system causing the block. It is not uncommon for heart block, which occurs in acute rheumatic fever and other acute infections, to be relieved by atropine. It is possible that in such cases there may be some change of vagal tone through altered physiology at the myoneural junction. Carter and Dieuaide[2] reported a case of recurrent complete heart block in which the P–R interval returned to normal with atropine, yet necropsy showed a badly diseased bundle.

Summary. A series of 100 cases of heart block with prolonged P–R intervals is reported. The study consists of a review of 6732 electrocardiograms taken on 4264 patients at the Lawson General Hospital. The etiologic classification of block is given with a discussion of causative factors. The P–R intervals of the 100 cases are tabulated, as well as variations in age and pulse rates. The normal range of the P–R interval is discussed. The belief is expressed that an occasional person may have a prolonged conduction time which is normal for that person and is perhaps associated with an individual variation of vagal tone. Observations are given regarding the effects of atropine in heart block with an expression of our beliefs as well as those of other observers concerning its use.

REFERENCES

1. Bayles, T. B.: Am. J. Med. Sci., **42**, 205, 1943.
2. Carter, E., and Dieuaide, F. R.: Bull. Johns Hopkins Hosp., **34**, 401, 1923.
3. Ferguson, D., and O'Connell, J. T.: U. S. Naval Med. Bull., **24**, 860, 1926.
4. Katz, L. N.: Electrocardiography, Philadelphia, Lea & Febiger, 1941.
5. Lewis, Sir Thomas: Mechanism and Graphic Registration of the Heart Beat, 3rd ed., London, Shaw & Sons, Ltd., p. 184, 1925.
6. Lewis, Sir Thomas: Diseases of the Heart, 2nd ed., New York, Macmillan, p. 94, 1937.
7. Pardee, H. E.: Clinical Aspects of Electrocardiography, New York, Hoeber, 1941.
8. Poel, W.: Arch. Int. Med., **69**, 1040, 1942.
9. Weiss, S., and Ferris, E. B., Jr.: Arch. Int. Med., **54**, 931, 1934.
10. White, P. D.: Personal communication.

NEUROPSYCHIATRIC CASUALTIES FROM GUADALCANAL

I. Persistent Symptoms in Three Cases*

By Major Albert A. Rosner, M.C., A.U.S.

Although 15 to 20% of war casualties reaching the United States are neuropsychiatric,[11] the relative proportion of these cases was much higher in the Guadalcanal Campaign. Forty per cent of the total evacuated to this country from Guadalcanal suffered from disabling neuro-mental disease. Only 5% of a comparable group from Pearl Harbor were of this type.[24] Smith,[24] under the title "Guadalcanal Neurosis," described these cases as a new and unique psychiatric malady. These soldiers were reduced to a pitiable state of military ineffectiveness after prolonged exposure under severest tropical conditions to exhaustion, fear, malaria, and sudden violent death at the hands of an insidious and ruthless enemy.

Three such cases, observed 10 months after leaving Guadalcanal are presented in some detail. The dramatic severity and persistence of a combat-incurred neurosis, similarity of symptoms, and absence of psychiatric irregularity in the pre-morbid personality are features of particular significance in these cases. In this paper are considered the immediate physical and psychologic elements responsible for mental breakdown in this group of soldiers.

Case Reports. Case 1. Age 27, born in a small manufacturing town in Massachusetts. Father: American born, high school graduate, considered a competent and efficient worker in a shoe factory. He is irritable, high-strung and addicted to alcohol. Divorced by patient's mother, who remarried. Mother: Born in Massachusetts; of normal temperament and disposition. There are 7 siblings, all living and well. There is no history of mental disease in the immediate or remote family line.

Personal History. Patient was born in the same Massachusetts town as his father. At the age of 2 he had infantile paralysis and was treated at a local clinic for some years thereafter. Minor weakness and atrophy of anterior tibial group of muscles of right lower extremity persist as residuals. No disability or gait disturbance. Active indulgence in sports of all kinds, including football during childhood years. Chickenpox and whooping cough at 8. Chorea, at 9, required temporary absence from school; no residuals. Progress at school irregular because of indifference, and interest in athletics and social diversions. No history of truancy, or difficulty with school or legal authorities. Left school during 8th grade. Patient was active in social affairs, well liked, and devoted to his many friends. Work record is excellent; worked steadily and efficiently at one job in a paper mill from the time of leaving school to date of induction, earning $32 to $35 per week. Married shortly after induction. In every respect marital relationship has been mutually satisfactory; patient considers himself happily married; desires children after the war. Army record is excellent. Became a private first-class. "I did not try to further myself. I was satisfied to be a soldier."

Present Illness. Patient was landed on the Guadalcanal beachhead in October, 1942 where he participated in the campaign to extend the beachhead and to capture Henderson Field. He suffered all the privations of active bitter

* This is the first of 2 papers on Psychiatric Casualties from Guadalcanal. A forthcoming contribution will concern a reëvaluation of the predisposition factor in neuroses of war.

jungle warfare. He witnessed the violent death of many intimate friends. For a time, his position was exposed to repeated bombing raids by enemy planes and to shelling by high-caliber naval guns by elements of the enemy fleet. Despite frequent malarial chills, he was maintained in front line fighting. Four weeks after landing at Guadalcanal, while his party was attempting to silence a Japanese machine gun nest, his position fell under direct fire of Japanese howitzers. Patient recalls distinctly that 2 shells exploded nearby almost simultaneously, one on either side of him. He was rendered unconscious, remaining so for 2 hours. He recalls, with difficulty, events of the following 2 weeks. He vaguely remembers being carried to a field hospital and then being evacuated by air to a hospital establishment on another island. Here he had an attack of malaria with severe chills and high temperature. Patient was then evacuated to a more permanent installation where, 4 weeks after his initial accident, he was seen by a psychiatrist. "I was nervous, shot to pieces and my head ached. I was mostly in a daze. I lost my memory a little part of the time. I could not remember my address." No associated nausea, vomiting or visual difficulties. Patient was then sent back to the United States. After months of rest, combined with active treatment in two general hospitals, patient was sent home on a 30-day sick leave. Patient was then put on a limited service status, with a diagnosis of psychoneurosis, anxiety type (battle reaction). He was then referred to our Training Center.

Because of irritability, headache, insomnia, difficulty in concentration, tremor and inability to perform even minor military duties, patient was referred to the Psychiatric Section of the Station Hospital for observation.

Examination. On admission to the hospital examination revealed a well proportioned individual of normal height and weight. Muscles were firm and well developed. Heart and lungs were normal. Abdominal examination disclosed no evidence of splenomegaly or hepatomegaly. Roentgenologic examination of chest and laboratory examinations, including numerous smears for malarial parasites, were negative. Icteric index was normal.

Neurologic examination disclosed minor residuals of old poliomyelitis in the right lower extremity. There was no apparent foot drop, however. In addition, fine regular tremor of the head and outstretched hands was present in moderate degree; increased perspiration was noted, especially when patient related his Guadalcanal experiences.

During interviews patient became anxious and voluble while discussing his symptoms. "It's too much for me. I get nervous when I get out there and have to give orders. I can't do it." Despite relatively recent return from a month's sick leave, patient states, "I'd like to get a leave, Sir. I'd like to go home for a while. I'd like to get an assignment closer to home. God knows when I'll get home again." Asked what assignment he felt capable of tackling, "I'd like to be a guard, Sir." Later, "I'd better take that back. You can't tell. I don't know about the gun part of it. I am afraid something might happen. I might hurt or kill someone." Patient trembled visibly. "You can never tell about fellows that went through Guadalcanal. Everything I hear makes me think of that place. I could not handle another rifle. The slightest noise makes me jump. I was once a good soldier, but not any more. I just cannot do anything. A fellow changes when he comes back from what I went through." Asked about a medical discharge, "I could use an army discharge, but I don't care." This patient, and the 2 others from Guadalcanal, were somewhat difficult to handle on the ward. The 3 were often reported for irregularity in conduct. On several occasions they were reported for failure to observe ward regulations. They were irascible, noisy, and at times frankly aggressive. Irregularities of this type, however, were by no means the rule. Otherwise, these patients were obedient, presentable and soldierly. Unpredictable and sudden change in attitude and behavior was quite striking.

All attempts to reclaim this soldier failed. Physical activity of any kind left him weak and trembling, and usually gave rise to headache. Indoor assignments were no more successfully performed. Patient failed in accomplishing the most trivial military duties. In July, 1943, 9 months after leaving Guadal-

canal while under observation in the hospital, patient suffered exacerbation of malaria with chills and high temperature. Tertian type malarial parasites were identified in the blood smear.

CASE 2. Age 23, born on a small farm in Missouri. Father was a tenant farmer in impoverished circumstances, though considered normal in temperament and disposition. Both parents were born in Missouri; both literate. Mother is considered stable and dependable. There are 4 siblings, all living and well. Patient is the youngest in the family. There is no history of nervous or mental disease in the immediate or remote family line.

Personal History. Patient was born on father's small Missouri farm. No known serious illness or injuries as a child. Patient began school at the age of 5, reached the 8th grade; left at the age of 15. Attendance record was good and there is no history of chronic truancy or of difficulty with school authorities. Had little difficulty learning, but was not particularly interested in obtaining an education.

He was arrested once at the age of 17 for writing a check for $6, but patient was not indicted and was released upon payment. No further difficulties with legal authorities.

Work record was fair. He worked for various neighbors on their farms and had various temporary jobs, such as truck driving during the harvest season. During these years patient lived at home with his parents. Was regarded as somewhat headstrong but otherwise was popular with boys of his own age group. No chronic social or sexual difficulties.

Married in 1940 at the age of 19, obtaining a divorce 10 months later. Separation stated to have been due to infidelity and uncongenial habits of his wife. Sexual habits were somewhat promiscuous after divorce. He contracted gonorrhea twice. Occasional overindulgence in alcohol, rarely to the point of intoxication. Army record is excellent. He has never been in difficulty with army authorities except on 1 occasion when company punishment was meted out for gambling. He was regarded as an aggressive, dependable soldier.

Present Illness. Patient was set ashore on the island of Guadalcanal with the first wave of troops landed in October, 1942. On the night of arrival, his position was shelled by units of the Japanese fleet, which paraded through the nearby bay lobbing high-caliber shells into the American position. This performance was repeated nightly. In addition, the small beachhead was subject to repeated raids by Japanese planes. The patient was active in the jungle campaign to enlarge the beachhead. Patient was tired, frightened and hungry most of the time. Sleeping and eating were irregular. He suffered from heat and humidity. Patient's life was repeatedly in jeopardy. At 5 o'clock one morning, a month after the initial landing, while preparing breakfast at his front line position, the patient suddenly became panic-stricken and began to shake all over. He cried constantly. "I felt like running. I did not care where. I just could not stand it where I was." He was removed, in this condition, from his foxhole to a point a few yards behind the forward position where he was seen within 15 minutes by a medical officer. He was then removed to an aid station. "From then on I don't remember anything until I woke up in a hospital the next morning. My head was hurting and my ears ringing." Patient had severe chills. A blood smear revealed the presence of malarial parasites. "Every time an airplane came overhead I would shake all over and my nerves would go to pieces."

Patient was then evacuated by plane to a hospital establishment on another island. After a week he was transferred to another hospital where he was seen for the first time by a psychiatrist—2 weeks after his initial breakdown. Patient was then returned to the United States. After months of treatment and rest in 2 general hospitals, patient was given a 30-day sick leave, following which he was placed on a limited service status. He was then referred to Basic Training Center No. 10, Greensboro, N. C. This patient, together with the 2 others herein reported, were together since their simultaneous arrival in the United States.

One of the patient's outstanding complaints was headache, despite the fact

that no concussion element was present. He complained of extreme nervousness, nightmares, inability to concentrate, extreme irritability, chronic weakness, fatigue and tremor.

Examination. On admission, examination revealed a well developed, well proportioned soldier of normal weight and height. Heart and lungs were normal and abdominal examination was negative. Roentgenologic examination and laboratory studies, including numerous examinations for malarial parasites, were negative.

Neurologic examination disclosed moderate tremor of the outstretched hands, and occasionally of the head. Increased perspiration was noted when he talked of his Guadalcanal adventures. Patient objected to having a blood test taken. Failed to coöperate in general ward routine. Generally overintimate with various female employees. During neurologic examination, overreacted markedly to such stimuli as pin-prick and tuning fork. During interviews appeared somewhat indifferent and cautious, answers being given in a somewhat stereotyped fashion. Manner at times was distinctly unsoldierly. He attempted to maintain an attitude of reserve but, while talking, agitation became more and more apparent.

When this patient was seen for the first time in the Neuropsychiatric Department his first words were, "Doctor, I am shell shocked." Patient stated that before coming ill he used to take great pride in exhibiting his prowess as a soldier; he talked, with pride, of how he stood up to 30 mile hikes with full field pack. "I could keep up with the best of them. I have a good attitude towards being a good soldier, but my condition won't let me be. I cannot drill with troops because my nerves tire easily, and I am weak all over. I cannot sleep at night. I cannot stand any noise. I am getting no better after all of these months. It's not helping me just being in a hospital." Later, "I could use a 6-months rest at home—not in the army." As to exaggeration of symptoms, "Why should I be a goldbricker? I should like to be classified as more than a goldbricker. A man who has been through what I have been has a right not to be called a goldbricker."

Case 3. Age 20, born on father's farm in Nebraska. Parents were in moderate financial circumstances. Father, born and educated in Nebraska, was a successful farm-owner and operator; dependable and stable. Patient's mother, also Nebraska born, is literate, sociable and well-considered by her neighbors. She is stated to be somewhat nervous and high-strung. There are 11 siblings, all living and well. No nervous or mental disease reported in the family.

Personal History. No serious illness or injuries as a child. Home was considered a happy one and patient recalls no chronic family or social difficulties. Began school at the age of 6 and graduated grammar school at 14. No failures. He was well-liked by teachers and playmates. Worked thereafter on his father's farm and occasionally for neighbors. He had many friends both male and female. Normal heterosexual adjustment. No legal difficulties of any kind. Work record is excellent. His National Guard organization was federalized in 1941. He was considered a stable and utterly reliable soldier.

Present Illness. Patient landed on the beachhead at Guadalcanal in October, 1942. His experiences were similar in every respect to those of the 2 patients already described. In addition, the patient is known to have had 3 attacks of malaria, about which he states, "I did not worry so much about the airplanes as I did about the malaria. It left me weak and tired." In November, 1942, a month after arrival at the island, a bomb exploded nearby, leaving him somewhat nervous and excited. He was removed temporarily from the front line area, but returned to full duty a few days later. Seven weeks after arrival at Guadalcanal a shell of large caliber landed in his vicinity sufficiently close to partially cover his foxhole with dirt and refuse. He recalls hearing the shell explode, but nothing else. Three hours later he regained consciousness, suffered severe, splitting headache, dizziness, vomiting and nosebleed. He was seen on the spot by a local medical officer. He could not be evacuated immediately and remained at the front all night under shell fire. He was evacuated the

next day and then taken by plane to another hospital establishment. He was then transferred to another island, where he remained about 1 month, complaining of headache, dizziness, nervousness, terrifying dreams, extreme weakness and fits of trembling. This patient was seen by a psychiatrist 8 days after his initial collapse. He was returned to the United States, and treated for many months in two general hospitals. Sent home on a 30-day furlough and then assigned to Basic Training Center.

Examination. Physical examination disclosed only tremor and increased perspiration. All laboratory examinations, including smears for malarial parasites, were negative.

In the hospital, patient was generally quiet and coöperative, though given to outbursts of increased activity from time to time. He seemed to prefer to remain alone. Patient was definitely depressed. "I feel weak and I have no energy. I have headache all the time. I cannot stand the heat. I get weak. I cannot sleep. I have nightmares that wake me up. I still jump when I hear noises, especially airplanes. When you get something like that in you it is hard to get it out. They used to bomb us all day long. I cannot take it any more. I cannot get out there on the drill field. I cannot think fast. I cannot do what I used to do." Asked about an easier assignment. "I don't feel that I am good for anything—I honestly don't feel I can be useful. I used to like the army, but since Guadalcanal I lost all of my friends and I don't care about it any more." Later, "It bothers me to be around soldiers all the time. They get me nervous. I used to be able to do anything. I am not a goldbricker or anything like that. I was in the army 2 years and was on sick list only 2 times. I used to enjoy being with soldiers, but since I lost all of my best friends when they got killed I don't any more. I blame it more on malaria fever than anything else. I had it 3 times." Frequently tearful.

Discussion. Since World War I, neurosis incurred in war time or under combat conditions has come to be considered pre-conditioned and non-specific. The term "shell shock" for example is supplanted by the less suggestive and less militant "anxiety neurosis"; similarly "gas neurosis" becomes "acute psychoneurotic respiratory syndrome."[20] There has been deëmphasis of exciting cause and reëmphasis of individual personality and other predisposition factors.[1-3,6-10,13-16,18,19,21,22,25-27] It is odd to discover, therefore, in modern milito-psychiatric literature a condition designated by the title "Guadalcanal Neurosis." The use of this term represents a reversion to concepts now unfashionable concerning the origin of the so-called war neuroses. Whether this condition, as described by Smith, represents a new disease appears less important than the circumstances that gave rise to it; the brutal combat situation responsible for this interesting psychiatric aberration, however, redirects attention to the importance of exciting cause.

In contrast to the much larger group of soldiers who, because of predisposition, influence of poor family history and psychiatric irregularities, break down early in the course of their military careers,[12] these soldiers broke late, and then only under extreme combat conditions. Among the British during the second Libyan Campaign of 1941,[15] and among the Americans in the North African Campaign,[7] predisposition factors are reported to have been prominent among neuropsychiatric casualties. On the other hand, the majority of acute neuropsychiatric states noted during and immediately following the Dunkirk evacuation occurred in soldiers of normal stability and adjustment;[23] response to treatment was immediate and gratifying.[4] A

somewhat similar situation obtained among bombed civilians of Barcelona and London.[17] In contrast, absence of neuropathic taint and failure to respond satisfactorily to treatment characterize a certain proportion of the Guadalcanal group.

The incidence of a severe and deeply rooted neurosis in individuals not otherwise disposed to mental illness invites attention. This is particularly true in view of prevailing emphasis on the importance of predisposition factors in the psychogenesis of neuroses in war.

Summary. 1. Three typical American soldiers of normal emotional and psychologic make up, whose family histories are generally free of neuropathic taint, under the stress of identical campaign and battle conditions have been rendered useless as a front line or support troops. Certain inherent and fundamental patterns of reactivity once regarded as normal, have been so shattered at Guadalcanal that judged solely on the basis of their behavior as soldiers subsequent to injury, these three at present fail to meet the standard of psychiatric competence demanded by army regulations. Their origins are diverse sociologically and geographically. Their behavior was regarded as normal in their respective communities, by their local board physicians, by their induction examiners, and by their superiors in the various stages of training in preparation for combat. Their army records reflect a high degree of adaptability. Only the accident of war and exposure to the exigencies of war exposed their common susceptibilities.

2. Their symptoms are not only similar, but are couched in the same phrases and intoned with the same inflections, with the same air of resignation and defeat. Headache, chronic fatigue and lassitude, tremor, insomnia, nightmares, restlessness, increased tension, hyperacusis, and inability to concentrate are common to all.

3. Behavior, as well as symptoms, is strikingly similar. They have at times been peevish, aggressive, demanding, and occasionally recalcitrant. On these occasions behavior stands in distinct contrast to that noted prior to the Guadalcanal Campaign.

4. All have been exposed to an extreme degree of exhaustion, fear, hunger, thirst, tropical heat and humidity, and jeopardy of life and limb.

5. All were debilitated by malaria before being rendered *hors de combat* by an acute neuropsychiatric disability. One patient suffered an exacerbation of malaria 9 months after leaving Guadacanal.

6. Two who were rendered unconscious concomitant with shell bursts exhibited no postconcussion or amnesia covering the event, and recalled with great clarity and detail, placement, sight and sound of the exploding shell.

7. Despite the absence of a specific concussion factor in one soldier, amnesia followed the onset of an acute neuropsychiatric condition. This may have been induced in part by the administration of drugs. In addition, this patient, as well as the others, complained of severe headache.

8. All were evacuated through identical medical channels and have been intimately associated for at least 8 months.

9. Neurological examination failed to reveal any evidence of focal neurologic disease with the exception of minor residuals of poliomyelitis in 1 patient. All 3 exhibited hyperhydrosis and tremor.

10. To date, almost 1 year later, symptoms persist with great tenacity despite active therapeutic measures.

REFERENCES

1. Aita, J. A.: Staff Meet. Mayo Clin., **16**, 294, 305, 1941.
2. Bigelow, R. B.: War Med., **2**, 381, 1942.
3. Cooley, M.: War Med., **1**, 372, 1942.
4. Denbenham, G., Sargant, W., Hill, D., and Slater, E.: Lancet, **1**, 107, 1941.
5. Editorial: Lancet, **1**, 299, 1940.
6. Editorial: Lancet, **1**, 222, 1943.
7. Extract No. 41*a*, Atlanta, School of Military Neuropsychiatry, Lawson General Hospital, 1943.
8. Fairbain, W. R. D.: Brit. Med. J., **1**, 183, 1943.
9. Gowan, L. R.: U. S. Nav. Med. Bull., **41**, 129, 1942.
10. Hadfield, J. A.: Brit. Med. J., **1**, 281, 320, 1942.
11. Halloran, R. D., and Farrell, M. J.: Am. J. Psychiat., **100**, 14, 1943.
12. Hecker, A. D., Plesset, M. R., and Grana, P. C.: Am. J. Psychiat., **99**, 33, 1942.
13. Hill, T. R.: Lancet, **1**, 332, 1943.
14. Lewis, A., and Slater, E.: Lancet, **1**, 496, 1942.
15. Love, H. R.: Med. J. Australia, **2**, 137, 1942.
16. Michaelo, J. J.: War Med., **2**, 172, 1942.
17. Mira, E.: Brit. Med. J., **1**, 1217, 1939.
18. Pegge, G.: Brit. Med. J., **2**, 553, 1940.
19. Pegge, G.: Brit. Med. J., **2**, 764, 1939.
20. Rennie, T. A. C., and Small, S. M.: Review Series, Vol. I, New York, Josiah Macy, Jr., Foundation, p. 1, 1943.
21. Rioch, D. McK., Jacobsen, C. F., Fingert, H. H., and Warson, S. R.: Psychiatry, **4**, 331, 1941.
22. Rodger, D. E.: Brit. Med. J., **2**, 351, 1943.
23. Sargant, W., and Slater, E.: Lancet, **2**, 1, 1940.
24. Smith, E. R.: Science News Letter, May 22, 1943. Read at annual meeting of Am. Psychiat. Assn., Detroit, May 10, 1943.
25. Simon, A., and Hagan, M.: Am. J. Psychiat., **99**, 348, 1942.
26. Simon, A., Hagan, M., and Hall, R.: War Med., **1**, 387, 1941.
27. Sutherland, J. D.: Brit. Med. J., **2**, 365, 1941.
28. Vernon, P. E.: J. Abnor. Psych., **36**, 457, 1941.

TUMEFACTION OF SUBCUTANEOUS FAT FOLLOWING THE INJECTION OF INSULIN

A Chemical and Histologic Study

By Hugo T. Engelhardt, M.D.
INSTRUCTOR
AND
Vincent J. Derbes, M.D.
INSTRUCTOR
NEW ORLEANS, LA.

(From the Department of Medicine, Tulane Univ. School of Medicine)

In spite of the fact that insulin has been in widespread use since 1930, no one completely understands its effect on subcutaneous fat following its injection. The results have been paradoxical because, on

the one hand, marked atrophy may follow and, on the other, fatty tumefaction may result. Alpert and Ferguson[1] (1939), reporting on a 7-year study of diabetics at King's County Hospital, found that 7.4% of their patients developed lipoid atrophy. Joslin and his associates[9] found that atrophy occurred in 18.4% of their series of diabetics.

Fat tumefaction at one time was held to be uncommon. As a matter of fact, Bader and Vero[2] indicated in their report in 1937 that only 1 previous case (Rowe and Garrison)[13] had been described in the American literature. Goldner,[7] in a recent review of the subject, states that only 18 cases had been reported in the world literature. We feel, however, that this phenomenon is not exceptionally rare. Previous attempts at study of these tumefactions appear to have been limited entirely to histologic examinations of biopsy material. We have been unable to find a chemical study of the constituents of these lipoid tumors. Marble and his group[10] conducted detailed analyses of the lipid material in fat atrophy. By the methods employed, no differences between normal and atrophic fat could be detected except a decrease in the amount of neutral fat in the atrophic area. In the case to be described, the opportunity for chemical study of lipomatous material was afforded.*

Case Report. The patient is a 12 year old white female who was first admitted to Charity Hospital when she was 2½ years old with the diagnosis of pneumonia, and was coincidentally found to have diabetes mellitus. She remained in the hospital for 2½ months and was regulated with much difficulty. In the intervening years, the diet was changed very little. Unmodified insulin was consistently given subcutaneously in the deltoid regions of both arms. After 2 or 3 years, swellings at the injection sites became apparent, and these increased in size slowly (Fig. 1).

Physical Examination. The patient is a well proportioned, intelligent white girl, not appearing ill, and definitely retarded in growth. The outstanding findings are bilaterally symmetrical enlargements overlying the deltoid muscles. These are at the sites injected with insulin over the 9½-year period. On palpation, these areas are rather soft, giving the impression of fluid under some slight tension. The borders of the masses blend with the surrounding subcutaneous tissues. The areas measure 8 x 6 x 3 cm. and exhibit none of the characteristics of inflammation.

The laboratory data are those customarily seen in uncontrolled diabetes.

Methods and Material. Using novocaine anesthesia and under aseptic precautions, a mass of material was removed from the center of the tumefaction overlying the left deltoid. For a normal control, fatty tissue was obtained from the abdominal panniculus of an individual who had met a sudden death. Both specimens were placed in containers filled with solid carbon dioxide and were immediately transported to the laboratory where the following procedures were undertaken.

The limited quantity of tissue samples available necessitated the use of the residual materials from the moisture determinations in ascertaining the percentage of total lipids present. The alcohol-ether extract was taken up in ether and filtered to remove traces of extraneous material. This filtrate, dried under vacuum, was divided into 3 portions and used as follows: (*a*) determina-

* We are indebted to Dr. K. S. Markley, Chief of Oils, Fat and Protein Division of the Southern Regional Research Laboratory, United States Department of Agriculture, for his assistance and particularly to Mr. B. A. Smith and Mr. F. G. Dollear who performed the quantitative chemical analyses.

tions of free fatty acids, saponification number, saponification equivalent, unsaponifiable material, cholesterol, and total fatty acids; (*b*) determination of iodine number; (*c*) determination of phosphorus.

FIG. 1.—Site and size of tumefaction.

Moisture. Four-gram samples of tissue were weighed into tared casseroles, minced with scalpels, the scalpels rinsed with alcohol and ether, and the solvent removed on a steam bath. The casseroles were transferred to a vacuum oven and dried to constant weight under a vacuum of 30 mm. at a temperature of 75° to 80° C. About 18 to 24 hours were required.

Lipids. The dried residues from the moisture determination were transferred quantitatively to Soxhlet extraction thimbles with absolute alcohol, followed by a small portion of ether. The samples were extracted in Soxhlet apparatus on a hot plate with absolute alcohol for 8 hours. The alcohol was evaporated and the extraction process repeated for a 12-hour period with anhydrous, fat-free ether. The ether was evaporated and the samples dried to constant weight in a vacuum oven at 60° C. under a vacuum of 30 mm.

Free Fatty Acids. Two and one-half gram samples of filtered lipids were weighed into saponification flasks, 50 mm. of hot neutral alcohol added, and titrated with freshly standardized 0.1 N alcoholic potassium hydroxide reagent to a pink color with phenolphthalein as indicator. The free fatty acids were calculated as oleic acid.

Saponification Number (*Koettstorfer Number*). These values were determined according to the "Official Tentative Methods of the American Oil Chemists' Society," revised to 1940.[12]

Residues from the free fatty acid determination, corrected for the alkali added in neutralizing the free acids, were used in this determination.

Saponification Equivalent. These values were calculated from the data obtained in the saponification number, according to calculations of T. P. Hilditch.[8]

Unsaponifiable Matter. The method used was that recommended by L. V. Cocks.[3] The samples used were the residues from the saponification number determination. The volume of alcohol in the flask was evaporated to approximately 25 mm. before extraction with ether.

Total Fatty Acids. Samples used were the aqueous layers and washings from the determination of the unsaponifiable matter. These solutions were collected in casseroles, the alcohol and water evaporated on a steam bath, and the residual soaps dissolved in water and again dried. The soaps were taken up in water and the fatty acids liberated with 1:3 nitric acid in a warm solution. The two layers were quantitatively transferred to a separatory funnel with water and ether. The fatty acids were then extracted with 3 successive treatments with small portions of ether. The combined ethereal extracts were washed free of mineral acids with water and dried to constant weight in tared flasks, first under a current of dried carbon dioxide, and finally in a vacuum oven.

Iodine Number (Wijs). Iodine numbers were determined according to "Official and Tentative Methods of the American Oil Chemists' Society," revised to 1940.[12]

Sterol (as Cholesterol). These determinations were made according to the method of Windaus.[15] The sterol fraction was calculated as cholesterol.

Phosphorus. Phosphorus determinations were made according to a method reported by H. W. Gerritz[6] and modified by use of a magnesium nitrate alcohol reagent for digestion of the sample.

Phosphatids. These values were calculated from the percentages of phosphorus with a factor reported by H. M. McLean and I. S. McLean.[11]

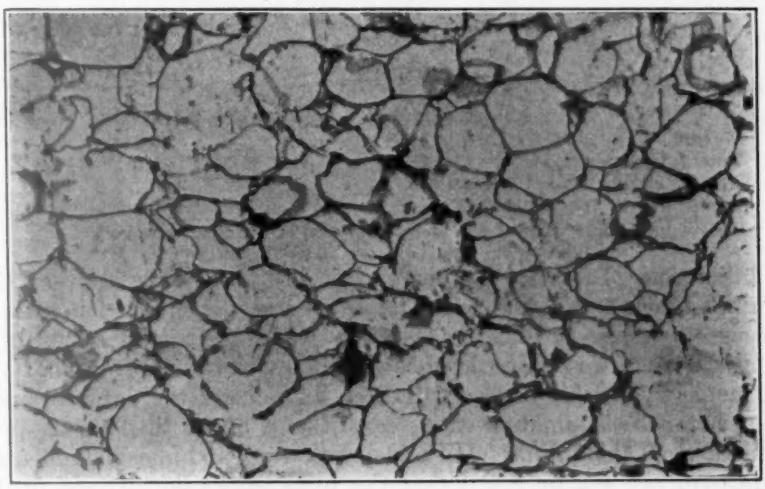


FIG. 2.—Section of biopsy specimen from area of tumefaction. (× 200.)

*Histologic Examination.** The sections (Fig. 2) show adipose tissue made up of fat cells of normal size and appearance. A few

* By Dr. Charles E. Dunlap, Assistant Professor of Pathology at Tulane Medical School.

fibrous trabeculæ are present in which blood-vessels and small nerves are seen. No inflammatory changes or other abnormalities are present. In short, this tissue is histologically indistinguishable from normal fat. Inflammatory reactions are inconstant, being reported by some authors and denied by others.

TABLE 1.—COMPARISON OF LIPIDS IN NON-DIABETIC AND DIABETIC TISSUES EXPRESSED AS PER CENT OF TOTAL MASS

	Non-diabetic tissue (%)	Diabetic tissue (%)
Moisture	17.8	23.4
Lipids (alcohol-ether extract)	79.6	70.1
Lipids (moisture-free basis)	95.5	91.4

TABLE 2.—COMPARISON OF LIPIDS IN NON-DIABETIC AND DIABETIC TISSUES WITH PARTICULAR REFERENCE TO THE CHARACTERISTICS OF THE LIPIDS

	Non-diabetic fat	Diabetic fat
Free fatty acids (as % oleic)	0.56	0.51
Saponification number	192.8	195.7
Saponification equivalent	290.9	286.7
Iodine number (Wijs)	69.6	70.3
Unsaponifiable matter (%)	2.88	1.89
Sterols (as cholesterol):		
As % of unsaponifiable matter	12.6	18.6
As % of fat	0.363	0.352
Total fatty acids (%)	92.2	92.7
Phosphorus (%)	0.027	0.023
Phosphatids (calculated from P determination)	0.582	0.683

TABLE 3.—COMPARISON OF LIPIDS IN NON-DIABETIC AND DIABETIC TISSUES SHOWING WATER CONTENT, TOTAL FATTY ACIDS, TOTAL CHOLESTEROL AND PHOSPHOLIPIDS

	Non-diabetic tissue		Diabetic tissue	
	As received	Moisture-free basis	As received	Moisture-free basis
Water* (%)	17.8	..	23.4	
Total fatty acids (%)	73.4	88.1	65.0	84.7
Total cholesterol, mg./100 gm.	289	347	246	321
Phospholipids, mg./100 gm.	463	556	479	624

* This value is approximate due to method used in handling samples.

Discussion. In Table 1 a comparison has been made between the normal tissue and the diabetic tissue as received in the laboratory. Because a significant difference* was observed in the amount of moisture in the normal and diabetic tissues, studies were made on the fats extracted by the use of alcohol ether. In Table 2 the data obtained from detailed examination of the constituents of the two fats are presented. In Table 3 total fatty acids, cholesterol and phospholipids are indicated. It will be noted that the total values do not add up to 100%, indicating that the tissues contained other constituents than water and fat.

It will be observed from examination of the data presented that there is very little difference in the non-diabetic and diabetic fats except in the unsaponifiable matter and phosphatids. These values

* Perhaps due to the greater amount of blood in the diabetic tissue.

are higher in the diabetic fat. Marble and Smith[10] arrive at a similar conclusion from their analyses of non-diabetic and diabetic tissue both in the human and the rat, except in the matter of neutral fat. They feel that the type of fat which disappears in fat atrophy is neutral fat.

An effort was made to present the analytical data in this report in such terms as to afford comparison with the data of Marble and Smith.[10] A review of their findings shows that those values reported as neutral fat were empirical and calculated from data not furnished. As the methods and data reported by Theis[14] represent values apparently differing from those to be found by Marble and Smith[10] calculations of neutral fat were omitted in this report.

It would seem then that the fat tumefaction in our case is composed of essentially the same constituents as non-diabetic fat, the difference being one of degree.

All writers on the subject appear to be in agreement that lipoid tumefaction following insulin appears chiefly in children. The explanation of this phenomenon remains obscure. Depisch[4] believed that it is due to repeated traumata at the same site, pointing out that in morphine addicts these changes are not observed because the site of injection is varied. It is of passing interest that one of us (V.J.D.) has not observed local tumefaction, although he has given many pollen injections at the same site over a period of years. Other explanations concern themselves with irritative substances in the insulin such as tricresol. The hypothesis that appeals to us is that of Gellerstedt,[5] who ascribes the phenomenon to a local physiologic assimilatory effect of the insulin, with localized fat retention. In our case, after the site of injection had been changed, there was a measurable reduction in the size of the tumefactions.

Summary. A case of localized fat tumefaction following insulin administration is presented. Detailed chemical analyses and histologic study are reported.

REFERENCES

1. Alpert, B., and Ferguson, E. A.: Endocrinology, **24**, 741, 1939.
2. Bader, G. B., and Vero, F.: J. Pediat., **10**, 185, 1937.
3. Cocks, L. V.: Analyst, **58**, 203, 1933.
4. Depisch, F.: Wien. med. Wchnschr., **80**, 168, 1930.
5. Gellerstedt, N.: Endokrinologie, **10**, 412, 1932; quoted by Bader, G. B.
6. Gerritz, H. W.: J. Assn. Off. Ago. Chem., **22**, 13, 1939.
7. Goldner, M. G.: J. Clin. Endocrinol., **3**, 469, 1943.
8. Hilditch, T. P.: Industrial Chemistry of the Fats and Waxes, 2nd ed., Van Nostrand, p. 44, 1941.
9. Joslin, E. P.: Quoted by Marble, A., and Smith, R., from unpublished work.
10. Marble, A., and Smith, R.: Proc. Am. Diabetes Assn., **2**, 173, 1942.
11. McLean, H. M., and McLean, I. S.: Lecithin and Allied Substances, The Lipins, 2nd ed., London, Longmans, p. 17, 1927.
12. Official and Tentative Methods of the American Oil Chemists Society, p. 31, 1940.
13. Rowe, A. H., and Garrison, O. H.: J. Am. Med. Assn., **19**, 16, 1932.
14. Theis, E. R.: J. Biol. Chem., **76**, 107, 1928.
15. Windaus, A.: Ztschr. f. physiol. Chem., **65**, 110, 1910.

PROGRESS
OF
MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF
IRVING J. WOLMAN, M.D.
PASSED ASSISTANT SURGEON (RESERVE), U. S. P. H. S.

MAJOR MOTILITY PATTERNS OF THE CHILD'S DIGESTIVE TRACT: A REVIEW

By Irving J. Wolman, M.D.

This Review aims to summarize present-day knowledge of major patterns of digestive tract motility in infancy and childhood. The sections of this report have been arranged according to the normal sequence of passage, commencing with sucking and swallowing and concluding with emptying of the colon. The original plan had been to focus attention exclusively upon the movement of food. But aerophagia and intestinal gas are such prominent features of this age period, especially in the infant, that appreciable space has been given to this subject also. Research studies of recent date have been selected as the bases for exposition whenever available, though older contributions have often been called upon to maintain the continuity of the account.

More comprehensive bibliographies than given here will be found in Peiper[86c] (swallowing); Henderson[44] (Roentgen ray appearance of stomach and intestines in newborn); Soveri[101] (aerophagia); Haas[36] (etiology of pyloric stenosis); Wolman[121] (gastric secretions); Kerley and LeWald[56] (roentgenology of digestive disturbances); Demuth[20] (milk digestion); and especially Freudenberg[28] (the older literature on digestion in childhood); and Alvarez[2] (survey of gastro-enterologic problems in general).

The principal source of information of alimentary movements has been roentgenology. In the following presentation the reader should understand that all descriptions of motility patterns were secured by this procedure, except when other techniques are specifically mentioned.

An analysis of the intricate neurologic mechanisms and chemical secretions which regulate motor activity has not been included. Presentation and evaluation of these complexly interacting influences would obscure the broad contours of normal motor function which this Review aims to portray. Furthermore, not much research has been done with reference to the distinctive functioning of these factors in children.

Descriptions of the almost numberless varieties of major anomalies and their symptom-complexes have also been omitted, except for congenital hypertrophic pyloric stenosis and a few lesser dysfunctions displaying altered gastro-intestinal motility as a dominant feature. McIntosh and Donovan[73] have discussed the derangements and disturbances resulting from anomalies in intestinal rotation.

Deglutition. Ingestion of food is the primary purpose of swallowing in man; but as Negus[77c] mentions, swallowing also removes the bacteria and secretions draining into the nasopharynx from nose, paranasal sinuses and middle ear. Similarly bacteria carried upwards from the lungs by ciliary action are swallowed, to be destroyed in the stomach. The act of deglutition or swallowing can be subdivided conveniently into three stages: buccal, pharyngeal and esophageal.

Mouth. In the older child, as in the adult, the mouth actions involved in eating and drinking are more or less under conscious and voluntary control.[77c] Food is grasped by the lips, masticated by combined action of tongue, teeth and cheeks, and forced back through the fauces by the curved arching tongue. This tongue movement seals off the pharyngeal lumen for the moment.

In the nursing infant, however, and particularly in the newborn infant, the nervous control lies on a lower more involuntary reflex level.[86c] Breast nursing, according to Peiper, begins with the "search" reflex[86c]—the restless head and lip movements exhibited by the hungry newborn when warm objects are placed in contact with or close to his face. On finding the nipple the baby presses his face firmly against the maternal breast, and the mother must press back her skin from the baby's nose in order that he may breathe while nursing. The sucking act itself has two phases: First the baby exerts suction by dropping the lower jaw; this draws milk from the depths of the mammary gland into the collecting ducts of the nipple, and may extract a little milk. Then the nipple and the tip of the breast becomes squeezed by mounting pressure as the lower jaw rises upon the upper, while at the same time stroking results from elastic retraction of the nipple and an opposing tongue movement. In this rhythmic coordination of jaw, cheek and tongue muscles the interaction of a number of distinct and different neuromuscular reflexes can be demonstrated.[86c]

In the infant fed from a bottle the movements of sucking are somewhat different. The rubber mouthpiece of the artificial nipple is less supple and yielding than the maternal nipple and usually projects more deeply into the mouth. With a rubber nipple, closure of the infant's jaw squeezes milk into the mouth; when the jaw relaxes the nipple resumes its original shape while air from the oral cavity rushes into the interior of the bottle. Other factors which help to eject milk into the baby's mouth are weight of the fluid column and momentary waves of "recoil" positive pressure as air bubbles rush into the bottle.[40,54,87] Generally speaking, the breast-fed baby has to work harder to get nourishment than does the one nursing from the bottle, except when the rubber nipple holes are very small.

Pharynx. In this second stage a peristaltic type of movement, involving the larynx along with the rest of the pharyngeal structures, thrusts the food from the palatine pillars to the esophagus. At the same time the esophagus opens and the normally lower intrathoracic pressure exerts a suction effect, particularly during inspiration. In fact, suction may draw food into the funnel-like mouth of the esophagus in advance of the peristaltic wave which descends to propel any lagging bolus.

The infant seems to be able to suck, swallow and breathe uninterruptedly for a long period of time without experiencing choking or other difficulty. The adult, on the other hand, must temporarily suspend respirations with every swallow, while the food flows across the laryngeal opening. This pause takes about 1.5 seconds.[17] The explanation for the difference between infant and adult swallowing, according to the traditional theory first proposed by Hasse,[41] is that the infantile larynx

rises high above the pharyngeal floor, so that fluid flows in lateral channels on either side instead of crossing the orifice. This would be analogous to conditions existing in herbivora and cetaceans who can eat and breathe simultaneously and in whom the elevated larynx reaches almost to the nasopharynx.[77]

When a hungry baby is given a feeding he sucks very rapidly, making 40 to 90 buccal cycles per minute for the first few minutes. Peiper[47,86b] studied the time relationships between sucking, deglutition and respiration in nursing infants by means of direct kymographic tracings and by Roentgen kymography. When the infant nurses steadily on a bottle, there takes place with each respiratory cycle either one sucking and one swallowing movement, or two sucking and two swallowing movements, or two sucking and one swallowing movement. The swallowing act takes place either in the instant between inhaling and exhaling, or the instant between exhaling and inhaling. During these split-second pauses the feeding flows over the larynx for from 0.15 to 0.18 second, the rhythm of breathing remaining unbroken. By snapping Roentgen ray films of infants during the moment of swallowing, using 0.05 second exposures, Hofmann and Peiper[47] were able to demonstrate radio-opaque feedings silhouetting the surface of the larynx. These observations fail to support the lateral channel theory of Hasse and denote that the intrapharyngeal mechanisms of swallowing in the infant are quicker but of the same nature as have been established for adults. Peiper[86d] points out that such quick acting coördinations between sucking, swallowing and breathing must be regulated by reflex centers in the central nervous system.

Esophagus. Food is driven through the esophagus to the stomach by peristalsis. Gravity furnishes but moderate assistance as is shown by the ease with which babies can nurse while in the supine position.

The mouth of the esophagus is normally kept tightly closed except when food is being swallowed. Otherwise the stomach would receive a fresh bolus of air many times a minute, one with each inspiration. A specialized band of fibers, the cricopharyngeal sphincter, fulfills the valvular function.

Peiper and Isbert[85] studied esophageal movements in infants by means of small rubber balloons placed *in situ*. During sleep or resting there were no peristaltic or tonus changes. In the waking state, under the conditions of the study, swallowing movements could be initiated by sucking on dry nipple.

Aimé and Lelong[1] studied in detail the appearance and behavior of the esophagus in 100 normal infants under $1\frac{1}{2}$ years of age. For the greater part of the interval between meals the esophagus was collapsed and empty. During deglutition the esophagus was found to have a lumen as wide as the shadow of the vertebral column. The shape was inconstant and changeable with slight curves and partial constrictions, ballooning out above the diaphragm when food was present. Swallowing liquids was always accompanied by an abundance of large air bubbles standing out clearly in the Roentgen ray films. With a thick meal of gruel or purée, in contrast, the quantity of air ingested was much less and the bubbles were small and sparse. Infants fed at the breast ingested as much air as did those fed on the bottle. After a meal, when the baby was upright, the esophagus often contained one or several sausage-shaped bubbles of air. In the horizontal position it was more likely to contain liquid material. The transdiaphragmatic segment measured about 1 cm. in length. When open it was tubular; when closed, invisible. To the authors it seemed

that the sphincter action here was accomplished by some external agency, such as the diaphragmatic crura.

Before the onset of clinical regurgitation waves of liquid would be seen to rise and fall within the esophagus, increasing progressively in height attained. Ultimately all the esophagus would fill and the upper sphincter open up to permit rejection of a little liquid by mouth. For every completed spitting-out there were many incomplete regurgitative movements. During regurgitation the esophagus was passive and ribbon-shaped, without constrictions, responding passively to the pressure from the stomach.

In the course of some 500 routine Roentgen chest examinations on newborn infants, Solis-Cohen and Bruck[100] frequently came across gaseous distention of the esophagus. These examinations were made about $1\frac{1}{2}$ hours after feeding time, when many of the infants no longer had a large bubble of air within the stomach. The authors theorized that this esophageal gaseous distention, which is a highly unusual finding beyond the neonatal period, was evidence of poor functioning of the cardio-esophageal sphincter.

Cardiospasm. The controlling mechanism at the esophageal-gastric junction offers no obstruction to the passage of food or fluid down the esophagus to the stomach, but does prevent loss from regurgitation in the reverse direction when the stomach is emptying. There is a question[77c] as to whether or not a true anatomic sphincter is to be found at the lower end of the esophagus, though Hurst[48] declares one can be readily demonstrated, in stillborn infants, as a ring of thickened musculature with thickening of the overlying mucous membrane. In any event, there is universal agreement that physiologic sphincter activity does occur at this spot, perhaps due to a special group of nerves locally,[57] or to local physical conditions in the form of positive intra-abdominal pressure,[77c] or to external pinching off by the diaphragmatic cruri,[1,50] or to pressure from the liver and distended stomach.[75] Release of this sphincter is necessary for eructation of swallowed air.

Cardiospasm, known also as esophageal achalasia,[48] or preventriculosis,[50] is the term applied to the clinical disturbance which results when the cardiac sphincter chronically fails to open during deglutition. Clinically the disease is characterized by long retention of food in the esophagus, with stagnation, dysphagia, pain in the chest, malnutrition, choking spells and distention of the esophagus demonstrable by Roentgen ray. Treatment consists in stretching the unrelaxed though not hypertrophied sphincter by means of mercury bougies. Though predominantly a disease of adult life, it has been observed in childhood.[6,30,104,118]

A temporary transient cardiospasm may at times occur in the newborn,[8,108,109] producing dysphagia, dilatation of the esophagus, regurgitation of food after a few minutes nursing with no gastric content in the vomitus, and interference with passage of food into the stomach. The spasm of the cardia can be easily overcome by passing a catheter a few times.

Stomach. *Movements.* Alvarez[2] whose contributions to the study of the mechanics of the digestive tract are many and well known has critically analyzed current concepts of gastro-intestinal motor physiology, with the objective of stimulating research on the many problems still in need of elucidation. The comments in the next three paragraphs are from his book.

The motor activities of the stomach are complex, consisting "of all sorts of combinations of waves, systoles, tonus waves, ripples and reversed

waves." The rhythm of contractions is highly inconstant, the combination of descending waves and local contractions being irregular and ever changing. In adult men gross waves called peristalsis proceed from the cardia to the pylorus at the rate of about 3 a minute, ending usually in a systolic contraction of the circular muscle of the pylorus antrum. Following a wave of contraction a wave of relaxation may follow and material may sometimes then leave the pylorus. But probably the most important factor in initiating gastric emptying is a different kind of slow tonic contraction involving the whole muscular wall and increasing the intragastric pressure. This type of contraction appears to be independent of the other waves mentioned above.

Food is held in the body of the stomach for considerable periods without becoming agitated. Kneading and mixing takes place only in the region distal to the incisura angularis, the pars pylorica. It is questionable whether there is a separate sphincter muscle at the pylorus. This so-called "sphincter" behaves as if it were simply the more thickened distal segment of the muscular coat of the pars pylorica. That the pylorus is not of great importance is indicated by the fact that animals[72] and men[96] get along well following its surgical removal.

Gastric emptying takes place probably only when intragastric pressure becomes greater than pressure in the duodenum. A number of local factors influence the relationships between the pressures in stomach and duodenum, the ones most studied being posture, mechanical stimulation from the meal itself, duodenal distention, small intestinal irritations, fat in the bowel, acid or alkali in the duodenum, consistency, chemical status and osmotic pressure of the food, postoperative trauma and excitation of the vagus or visceral nerves. Foods which are liquid or easily liquefied leave early, whereas hard foods, such as uncooked rice, are kept longer. Alvarez[2] comments that "long lists have been made of the length of time required by various foods for gastric digestions, but as yet it is not known what use the dietition should try to make of this information. . . . The main organ of digestion is the small intestine; attempts to spare the stomach only throw more work on the bowel."

The method most widely used at present for measuring the period required for the stomach to become empty after ingestion of food has been the roentgenology of opaque meals. According to published reports emptying time can be influenced by type[42] and size[110] of the meal, state of hunger,[49] environmental temperatures,[97] psychic influences,[107] exercise,[43] and reflexes from other portions of the gastro-intestinal tract.[84] Such substances and medicaments as enterogastrone,[34] atropine,[46] sulfapyridine,[79] dehydrocholic acid[43] and benzedrine sulfate[76] can inhibit or stimulate emptying of the stomach.

Shape. The child's stomach in the resting state, between meals, is contracted and empty except for a few milliliters of secretion and perhaps a small gas bubble.[1,91] A number of studies have been devoted to the roentgenologic appearance when filled with food containing a contrast medium, though Rogatz[91] reported the infant stomach and surrounding landmarks to be easily identifiable without the use of barium or bismuth. The stomach shadow after a meal consists of an upper gaseous portion and a denser lower shadow. A level fluid line usually separates the two portions. Shape, size and position have proven to be highly inconstant and changeable, differing from child to child and with size and consistency of the meal. Barium sulfate is a heavy substance. Its presence seems to cause deep sagging of the greater curvature contour.

Theile[106] thought the various appearances in infancy could be grouped into two main categories: (1) the "bagpipe" or pear-shaped form, with a large circular expanded fundus and a smaller narrow pylorus directed to the right; and (2) the "tobacco pouch" or retort shaped form, with an expanded upper portion and a narrow lower portion, often with the pylorus visible as a projection to the right.

Rogatz,[91] in addition to corroborating these two types of shadows, speaks also of the stomach contracting to a small circular or oval shape when a thick meal is fed, barely reaching the midline, never extending beyond, and with a very small air bubble or often none at all. This third contracted type is accounted for in terms of a "peristolic" function of the stomach. According to Rogatz, as soon as food enters the stomach the walls are stimulated to surround and grasp the food content (peristolsis). With a fluid meal the peristolic effort if excessive may result in vomiting of the gastric content. With a thick semisolid food, which is viscous and less mobile, vomiting is less likely to occur. The tonus of the gastric wall is greater with semisolid foods because less air is swallowed with thick foods than with liquids and consequently distention of the wall is less.

Wright[122] studied an older group, consisting of 250 normal healthy children from 6 to 15 years of age. The size and shape of the stomach varied widely at all ages, showing especially striking variation as puberty was approached. A "sink-drain" appearance was more common in younger children, a "sharp hook" in older children. In 42% the stomach lay above the crests of the ilium, in 42% below the crests and in 16% at the crests.

For the newborn, Henderson[44] reported that the shape assumed by the stomach immediately following a meal was inconstant from baby to baby, and presented different contours depending upon whether the films were taken prone, supine, oblique or erect. Shape and size were contingent also upon the amount of air present; if infants cried lustily during feeding, air in unusually large quantities would be swallowed. Feeding usually stimulated gastric contractions, as did change of position and massage of the abdomen over the stomach. As a rule, spontaneous contractions were seen only in the pyloric antrum, but were detected occasionally in the middle and upper thirds. Gastric emptying usually bore no relation to visible peristalsis. Deep contractions might cause no evacuation into the duodenum whereas sometimes when no definite waves were visualized considerable amounts of barium would leave the stomach. Recognizable spasm of the pylorus was seen but rarely.

Gastric Emptying; Factor of Variability. That the stomach and intestines are subject to lack of regularity in their responses is common knowledge, but the extent of this variability in childhood has not been exhaustively worked out.

Todd and Kuenzel[107] found that for accuracy in adult investigations on emptying of the stomach one must use only trained individuals under adequately controlled conditions. Subjects must be willing, coöperative and familiar with the procedures. Otherwise confusing and inexplicable variations in response will be encountered. Mental disquiet or emotional stimuli are potent factors in causing pronounced alterations in the gastric responses.

Van Liere and Northup[111] have recently reëmphasized that test meals taken for study of normal gastric emptying have not been uniform in character or quantity. These authors suggested the general adoption of some one standard meal such as cooked farina 15 gm. in 350 cc. of water

boiled down to a volume of 200 cc. and then mixed with 50 gm. of barium sulfate. When they gave the above meal to 69 healthy male subjects aged 20 to 30 years under standardized conditions of relaxation after overnight fasting, variations were found ranging from 1.5 to 3.3 hours with a mean of 2.13 hours. Although on repeated testing many subjects exhibited remarkable constancy in gastric emptying time, others showed extensive fluctuation. One apparently normal individual had a range from 1.75 to 3.5 hours in tests repeated at weekly intervals. Hence criteria established for gastric emptying must be expressed as a zone of expected fluctuation rather than in rigid absolute figures.

The normal variability of the gastro-intestinal responses during childhood was examined by Macy, Reynolds, Souders and Olson.[65] The subjects of their study were 7 normal boys and girls aged 74 to 117 months who for months had been subjected to the same standardized conditions of adequate diet and living routine. They were thoroughly familiarized with the procedure of being roentgenologically studied, and remained emotionally calm during examination. Under controlled circumstances, about 1 week apart, test meals consisting of 2 ounces of barium sulfate mixed with 4 ounces of water or of milk were given; 18 months later the milk barium series was repeated. The results can be tabulated as follows (in hours):

	Gastric emptying time		Emptying time of jejunum	
	Range (hr.)	Mean (hr.)	Range (hr.)	Mean (hr.)
Water	1.0–2.8	1.9	1.3–3.0	2.4
Milk	1.5–4.5	3.1	2.0–4.5	3.4
Milk (18 mos. later)	2.5–4.0	3.6	1.0–4.0	3.2

Similar wide variations were observed in the rate of progress of the meals through the remainder of the intestinal tract, though variations among the different individuals were not as great as the differences between the water and milk meals. Note the great dissimilarity of the responses to the milk-barium meal after the 18 month interval. It is interesting that there were no consistent differences in the ultimate emptying of the colon as shown in roentgenograms made 24, 48 and 72 hours after the ingestion of the meals. No relationships to age were noted. The authors unfortunately did not perform repeat studies on the same child utilizing the same test meal in a shorter more comparable period than 18 months. The results of their tests indicate that the rate and pattern of normal gastro-intestinal motility as revealed by barium depend not only upon the nature of the test meal, but differs appreciably from child to child. To the Reviewer it seems not unlikely, on the basis of a few personal observations made with the stomach tube, that the range of normal variation for any one individual from day to day may perhaps be as great as the range Macy *et al.* encountered from subject to subject. No large group of children has been studied from the standpoint of extent of individual variation, in a fashion similar to that of Van Liere and Northup[111] with young adults.

In preparing the present discussion on gastric emptying it was found impossible to compare the findings of most investigations with each other. There were great differences in the character and size of the test meals and in the age, sex and constitution of the subjects themselves. Most studies seem to have paid little or no attention to elimination of psychologic effects, in spite of the disturbing element this factor represents.[107] Again the criteria taken to mark the moment of emptying

have been far from uniform. Some workers recorded the time when most of the food has been passed, though some radio-opaque particles still clung to the mucous membranes; others waited until the stomach had emptied itself completely. In most instances the observations were spaced too far apart—½ to 1 hour intervals—giving the data a great margin of error. Most series of cases were small in magnitude and lacked duplicate determinations for each subject for each test meal as the measure of experimental error.

Furthermore, the results of most studies on comparative emptying times have not been analyzed according to rigid statistical methods. In many experiments comparing one type of meal with another the variations among individual subjects receiving the test meal were of greater magnitude than the difference between mean values for experimental and control emptying times; in such circumstances the number of subjects used must be of appreciable size for any valid conclusions to be drawn. Thus, for example, Hadary, Sommer and Gonce[37] have questioned the conclusions drawn by as careful a group of experimenters as Reynolds, Macy and Souders[90] on the gastro-intestinal Roentgen ray responses of 7 children to test meals of pasteurized, evaporated and base exchange milks. They subjected the data of Reynolds *et al.* to statistical evaluation by the analysis of variance and concluded that the differences in motility times reported for these three milks had not been proven.

Because of the many differences in the test procedures, and since in most reports the number of cases has been small and not well controlled, results of but a few of the more thorough and representative investigations have been summarized in the paragraphs which follow. These show that the trend in the gastric evacuation pattern as the child grows toward puberty is in the direction of gradually extending the gastric evacuation time, save in the first few weeks of life, when complete emptying is sluggish and surprisingly prolonged. In all instances barium was incorporated into the test meal as the contrast substance.

In the newborn Henderson[44] observed that rapid emptying would take place while meals were being taken, to be followed by an interval of diminished motility for an hour or more and then peristalsis and evacuation. As a rule, most of the meal had moved on by 1½ to 2 hours. Eighty of 110 infants displayed gastric barium shadows after 8 hours and 30 of these still had some remaining at 24 hours. Similarly Findlay[24] studied 12 normal infants under 2 months of age with a milk meal as controls for a pyloric stenosis series. Barium was frequently visible in the duodenum in the film taken immediately after feeding. Nearly all retained large quantities of barium at the 2 hour examination; traces were often visible on the stomach wall after 6 hours.

Krüger[58] noted that for 11 breast-fed infants the emptying time was 2¼ to 3½ hours after feeding, whereas for 14 artificially fed infants the range was 2½ to 5½ hours with a mean of 3¼ hours. Theile[106] reported on a group of 11 breast-fed babies given successive meals of breast milk and of a half-strength cow's milk mixture. In nearly every case the breast milk evacuated earlier. The emptying time for the breast milk was 2 to 3 hours, for the cow's milk mixture 3 to 4 hours. He noted that feedings small in volume remained in the stomach as long as regular sized feedings. Frollo[30] studied 8 infants 1½ to 5 months of age with a milk meal. He reported beginning emptying within a few minutes and complete emptying by 3¼ hours.

Bouslog, Cunningham, Hanner, Walton and Waltz[11] reported on 133

infants aged 1 week to 6 months receiving a routine milk feeding mixture with barium. Films taken immediately after completion of the meal showed the presence of food in the small intestine in 244 out of 281 examinations. The emptying times for their series of 133 infants after the completion of the barium meal is shown in the following table:

	No.	%
Empty at 1½ hours	5	2
Emptying time from 1½ to 3 hours	27	9
Emptying time 3 to 5 hours	56	19
Emptying time 5 to 8 hours	80	27
Emptying time more than 8 hours	123	43
Total number of examinations	281	100

Buchheim,[12] with 23 subjects 1.5 to 14 years of age, found that applesauce began to leave the stomach promptly after ingestion, and that in 1 to 3 hours complete emptying had been achieved. Hainiss and Surányi[38] noted with 40 children, aged 3 to 10, having low blood pressure (systolic 88 or lower) that 35 showed delayed evacuation of the stomach, evidenced by the stomach contours appearing one-half filled 3 hours after ingestion of a barium meal. The arterial hypotonia and slow gastric motility were interpreted as symptoms of disturbance in function of the sympathetic nervous system.

Macy, Reynolds, Souders and Olson[65] studied 9 children, aged 4½ to 8 years, who for months had been subjected to the same standardized conditions of adequate diet, healthful routine and favorable environment. With a series of test meals fed at weekly intervals the following data were obtained:

	Range of variation (hr.)	Mean (hr.)
Water	1.0–2.8	1.9
Milk	1.5–4.5	3.1
Meat	3.0–7.0	5.0
Cream	2.5–6.5	4.8
25% corn syrup solution	3.0–4.0	3.3

The slow emptying time of the carbohydrate meal was ascribed to the high osmotic pressure, a factor which is known to slow gastric emptying. Carmine, 0.2 to 0.3 gm., was given to 7 of these children in another series of tests 3 weeks apart.[66] The average emptying time of the stomach was 257 minutes with the test meal alone; with the test meal preceded by the carmine the average was 177 minutes. However, the later progress of the carmine-containing meal was slower, so that the emptying times for the digestive tract as a whole were about the same for the carmine-barium meal as for the control.

Hadary, Sommer and Gonce[37] recorded gastric emptying times for 7 children between the ages of 4 and 13 given 5 different milk drinks—pasteurized milk, homogenized milk, chocolate milk, base exchange milk and reconstituted evaporated milk. On statistical analysis of the data no significant differences in evacuation time were noted among these milks. By 2 hours the stomach shadows had become reduced from 80 to 25% in scattered fashion, by 4 hours a good number were empty, and by 5 and 6 hours only a very few still contained residue.

Congenital Hypertrophic Pyloric Stenosis. The gastric motor disturbances consist of projectile vomiting, delayed emptying with prolonged retention of food, great peristaltic waves visible through the abdominal wall, abdominal cramps and constipation. The chief anatomic features

are muscular thickening of the pylorus and hypertrophy and dilatation of the entire stomach itself. The cause is as much a mystery as when the condition was described in 1777 by George Armstrong.[26] Of the hypotheses proposed in explanation, the more important seem to be: (*a*) the anatomic, which holds that the pyloric sphincter hypertrophies because of the relative obstruction caused by a malformed elongated canal[39] or from anomalous attachments of the pylorus;[21] (*b*) the neurogenic, which postulates an overstimulation or imbalance of the vagal sympathetic equilibrium as the incitement to pyloric hypertrophy and spasm;[3] and (*c*) the constitutional or hereditary hypothesis which postulates genetic bases in view of the high frequency shown by siblings[92] and the greater tendency for unovular twins than fraternal twins to be affected.[27] There is no explanation why the condition is more common among first-borns (52% of Robertson's[92] 278 cases were first-borns, whereas but 41% of the infants born in Toronto in that year were first-borns), nor why four-fifths of all patients are males.

The pyloric disturbance must have its origin *in utero*, for well-developed tumors are often encountered clinically and at operation in the first 10 days of life and in prematures. The lesion has even been found in a 7 month fetus, as described by Cautley and Bent.[14] Hence it seems proper to regard pyloric hypertrophy as a *congenital* lesion, with associated spasm developing in the 2nd to 5th week to produce the vomiting and allied symptoms. The presence of the tumor itself is not the sole factor in the production of disturbances, as shown by the sporadic cases in which little or no vomiting occurs,[7,74b] the scores of patients who have been relieved by thick feedings and phenobarbital, atropine or eumydrin,[63,112,113] and the persistence of characteristic radiologic changes for some years after all clinical phenomena have subsided under non-surgical treatment.[95]

Roentgenography has been repeatedly resorted to in the study of suspected cases of pyloric stenosis. The conclusions of different observers are not in agreement with regard to delay in emptying time. Thus, Findlay[24] compared by Roentgen ray 12 infants having hypertrophic pyloric stenosis with 12 normal infants as controls. In hypertrophic pyloric stenosis the onset of passage of the meal into the small intestine was delayed usually, sometimes from 30 to 60 minutes, yet in some undoubted examples later verified by operation the opaque meal entered the duodenum at the same rate as in the normal child. Final emptying was prolonged as a rule. Thus no sharp line of distinction could be drawn between the infants with pyloric stenosis and the normals. In the patients treated by pylorotomy, roentgenograms after 4 weeks showed motility and emptying back to normal. In those treated medically with eumydrin, however, as long as 6 to 8 weeks after all symptoms had disappeared positive Roentgen ray findings when originally present were still persistent.

On the other hand, Calvin and Denenholz[13] reported that with a test feeding of 2 ounces of milk containing 2 tablespoons of barium sulfate, hypertrophic pyloric stenosis could almost always be differentiated from pylorospasm by the relative amounts of barium in the stomach and small bowel after 4 hours. In 51 of 55 cases having stenosis, established by later operation, the stomach showed residual retention at 4 hours of 60 to 100% of the barium meal, as estimated from the shadow size. In 23 other cases having pylorospasm as shown by subsequent clinical course only 2 had more than 25% retention at 4 hours.

Meuwissen and Sloof[74] described visualization of the pyloric canal when the child is Roentgen rayed lying on the right side following a barium meal.

In normal children the length of the canal was but 1 to 2 mm. In 7 cases with severe clinical symptoms and treated by operation the length was 16.5 to 24 mm. In most of these the stomach showed delayed evacuation, though several were one-half to three-fourths empty before 4 hours were up. The contrast shadow of the pyloric antrum stopped abruptly at the pyloric canal and had a clear linear contour. In 7 other cases the canal was shorter, 4 to 11 mm. Only 2 of these were operated on; the others recovered from the vomiting and other symptoms with non-surgical treatment. It is interesting that in some patients the pyloric canal at times appeared fine and narrow, at other times wide and filled. These changes were ascribed to contraction and relaxation of the pyloric muscle. The authors concluded that intermediate borderline cases are not uncommon and that when the pylorus length is more than the critical length of 6 or 7 mm. the clinical picture of pyloric stenosis becomes strongly evident. In the opinion of Jochims[51] and Runström and Wallgren[95] this finding of an elongated pyloric canal is a much more reliable diagnostic sign of pyloric stenosis than are prominent peristaltic waves, delayed emptying time or enlargement of the stomach. Runström and Wallgren[95] reëxamined within a year 8 of 22 patients having the clinical features and the above diagnostic Roentgen signs. The appearances on the whole were unaltered, though the pyloric canal was perhaps broader at times and longitudinal folds more prominent. The stomach was still hypertrophied and gastric waves could be seen. Of 96 other children age 1 to 9 years who had once been diagnosed as hypertrophic pyloric stenosis and were now symptom-free, all but 4 still had an abnormally long pyloric canal, though patulous.

The stomach does not return to normal functioning instantly after operation. Faber and Davis[23] followed roentgenographically 10 pyloric stenosis babies. On receiving 1 teaspoonful of barium sulfate in 1 ounce of water within 1 to 5 hours after the Fredet-Rammstedt operation, complete gastric retention lasting from 3 to 11½ hours was noted in all. Emptying began 5 to 18 hours after operation and was not completed until about 20 hours postoperatively. In only 1 infant was the test repeated after the first postoperative day. This infant had slow emptying on the 3rd day but by the 20th day was quite normal. Bau[4] Roentgen rayed 76 children 8 years after operation for pyloric stenosis. In no case did the stomach present any pathologic condition attributable to the operation.

The general conclusion to be drawn from perusal of the many reports is that the Roentgen ray offers real aid in diagnosis. However, like most other laboratory tools, there is a significant margin of error. Findings must be evaluated clinically in the light of the other evidence at hand in the individual case.

Pylorospasm. Pylorospasm is a diagnosis applied rather freely and uncritically to the recurrent projectile vomiting shown by infants in the first few months of life. The forceful vomiting has been believed to be due to a dysfunctioning tautness of the pyloric musculature. Exit of stomach contents into the duodenum consequently is hampered. Undernourished children may display prominent peristaltic waves visible through the abdominal wall. The differential diagnosis between simple pylorospasm and hypertrophic pyloric stenosis has been summarized by Parmalee,[82] who disagrees with the older opinion, still sustained by Haas,[36] that many cases diagnosed as pylorospasm are essentially mild forms of congenital hypertrophic pyloric stenosis. Meuwissen and Sloof's[74] observations corroborate the latter view.

The factors responsible for the symptoms seem to be varied and multiple.

Unquestionably many cases loosely diagnosed pylorospasm owe their symptoms to excessive aerophagy, or to allergy, or to constitutional hyperexcitability, or to gastric irritation from faulty prepared feedings. Modern physiologic concepts of the gastric emptying mechanism are very different from the former orthodox conception of the pyloric sphincter as a "gate keeper." Employing new investigative methods on dogs, Quigley[88] and others[105,117] have obtained evidence indicating that the entire pyloric sphincter region normally executes rhythmic contractions and tends to behave as a unit. The sphincter seems to act in a manner similar to, not contrary to, the action of the antrum and bulb. Normal gastric evacuation is dependent on a pressure gradient from stomach to duodenum adequate to overcome the evacuation resistance. The pyloric sphincter lies open much of the time, even when the stomach is filled with food. During the act of emptying the resistance offered by the sphincter while contracting yields before the greater pressure developed by the pyloric antrum. The presence of foodstuffs or hydrochloric acid in the upper intestine retards gastric evacuation by depressing gastric motility. This retardation occurs in spite of a simultaneous depression of the sphincter and bulb. Emotional states and noxious stimuli delay evacuation by suppressing gastric motility and not by producing pylorospasm.[9] No recent survey has been found applying these new ideas to study of the pathogenesis of the recurrent vomiting in the infantile pylorospasm syndrome.

Aerophagia; Air in the Stomach. During infancy and early childhood gas in large amounts is present within the entire gastro-intestinal tract, from stomach to rectum. The chief source of this gas is neither fermentation of food nor diffusion from the blood stream, but swallowing of air. Proof lies in the chemical composition of recovered specimens, which have about the same nitrogen content as the atmosphere,[53] and in the demonstration that patients or animals having esophageal obstruction and fed through gastrostomy openings exhibit no gas in the alimentary canal.[115] Calculation from Charles' law brings out that room air at 21° C. will increase about 6% in volume on being warmed to internal body temperature—an expansion hardly of clinical importance.

Thiele[106] first demonstrated that air reaches the stomach and small bowel in the first 30 minutes of life. Later Bouslog[11] by roentgenography at the delivery table detected air entering stomachs of newborns with the very first inspiration. Paine and Nessa[81] found air in the stomach or duodenum within the first 10 minutes in 5 out of 7 newborn infants; air reached the sigmoid or rectum in all by 4 to 6 hours after birth.

Aimé and Lelong[1] and Soveri[101] as well as many older authors have carried out extensive studies on the entry of air into the gastro-intestinal tract of babies. In the period between meals the infant's stomach contains a small quantity of gas; after a fast, none at all. When a feeding is given by stomach tube no air bubble is formed. Gas does not become evident in the stomach when the infant nurses on the thumb or an empty bottle, because no swallowing takes place, except of saliva to a negligible degree. Air reaches the stomach only during swallowing. There is no retrograde current of air during the process of swallowing; evacuation by belching takes place only when the child is not swallowing. Adults differ from infants in being able to swallow air very readily, independently of eating, as demonstrated by Magnusson.[69]

After a feeding the baby's stomach usually contains a great gastric bubble ("magenblase") which disappears on eructation.[25] The reason

why infants fed on milk swallow more air than older children seems to be that liquids from a bottle reaches the throat in droplet quantity whereas solid foods form large boli which more completely fill the pharynx during deglutition. Since the stimulus for reflex contraction of the swallowing muscles is the impact of food particles on the posterior pharyngeal wall, bubbles of air from the pharynx are pushed down the esophagus with each swallow of milk.[1,77c] The shape of the nipple plays no rôle, since the source of the swallowed air is the nasopharynx and not the mouth. The position of the child during nursing, whether lying, erect, prone or supine, bears no influence on the size of the gas bubble which forms. Frollo[30] was so impressed by the quantity of air which can accumulate in the first few minutes of feeding that he postulated a muscular relaxation and drop in peristolic tonus taking place in the stomach wall, stimulated by reflex impulses initiated by swallowing. According to Theile[106] the shape and size of the stomach after a meal depends largely upon the amount of gas present.

There is disagreement in the literature as to whether the gastric gas bubbles are larger with bottle-fed babies. The differences observed would seem to be resolvable in terms of the size of the holes in the artificial nipples and the time spent in nursing from bottle or breast. Since each swallow of milk carries with it a bolus of air, the longer and more energetically the baby sucks the greater the gas bubble. If the nipple holes are so small that milk cannot flow freely from the bottle, air swallowing becomes prolonged and pronounced. Yllpö[123] had noted, by weighing breast-fed infants continually during nursing, that more than 80% of the milk was taken during the first 2 minutes. By 10 minutes more than 95% of the amount secured in 20 minutes would be taken. Yllpö demonstrated further with some 60 breast- and bottle-fed infants that the stomach gas bubble was much smaller when the feeding time was cut to 2 to 6 minutes in place of the customary 20 minutes. This change eliminated abdominal symptoms arising from mechanical disturbances due to gas, gave rise to no gastro-intestinal complaints and saved much time for the mothers and nurses. Rubber nipples must have large holes 2 mm. in diameter for such rapid feeding.

In the infant the pylorus lies caudal and anterior to the cardia. Hence, when the baby is held prone or semi-erect, the cardia lies at a higher level and the air will rise into it. Smith and Le Wald[98] have published serial roentgenograms which demonstrate the enormous bubbles which collect during feeding, to escape by eructation following postural manipulation. But when in the supine position air in the stomach rises toward the pylorus and is trapped by the gastric fluid. Thus food which passes from the stomach has to force air ahead of it into the duodenum. It is likely that swallowed air keeps leaking intermittently through the pylorus at all times.

Magnusson and Engström[68] found that the quantity of gas in the intestine of infants was greater when the children were prevented from belching after meals and placed on their left sides. Aimé and Lelong[1] observed that if immediately after nursing an infant is placed on the left side, the liquid contents settle to the fundus and the air rises toward the pylorus. In less than ½ hour the prepyloric bubble evacuates into the duodenum, not explosively but gradually. Conversely if the infant be placed on the right side the liquid accumulates near the pylorus and the gas rises toward the cardia, and the esophagus will open into air or liquid, depending on the relative proportion of each. They advised that infants troubled with

excessive abdominal gas be placed in the left lateral position for the first ½ hour following nursing and then on the right side for the next hour or two.

Soveri[101] reported that an infant's empty stomach can evacuate into the intestine 200 to 300 cc. of air within ½ hour, much of it being passed within 5 minutes. When the stomach contains a feeding and overlying air, the size of the bubble becomes reduced in size at an equal rate with the passage of the liquid content. When the feeding has been entirely evacuated the air bubble will be gone also.

To be distinguished from normal aerophagia, which occurs normally during deglutition, is excessive or hyper-aerophagia which can give rise to vomiting, colic and tympanites. The most common causes for this, according to Magliano and Hansen,[67] are nasal obstruction, even from simple coryza, feeble nursing, harelip, or cleft palate, and slow flow of milk from the nipple. It is recommended that such patients be treated by forcible belching every few minutes, the attendant exerting light manual pressure upon the abdomen. That aerophagy in excess can give rise to vomiting and other symptoms of gastric distress has been emphasized repeatedly, chiefly by foreign writers.[32,60,70,109a]

Small Intestine. *Duodenum.* In infancy, as the stomach empties, the first portion of the duodenum becomes filled as a more or less straight horizontal tube. The second and third portions are seldom visualized due to more rapid activity. When seen these resemble the first portion. The triangular Roentgen ray cap so familiar in the adult organ is rarely seen. With duodenal obstruction resulting from anatomic causes such as constriction by the mesenteric pedicle, the dilated duodenum will fill and stay filled with barium up to the obstructive site.[62] In such cases flat abdominal plates, without barium, may show the enlarged segment distended with a sausage-shaped accumulation of gas.

Cohen[18] has pointed out that plain roentgenograms of the gastrointestinal tract of newborn babies having congenital duodenal obstruction will show the column of air cut off at the site of obstruction, with gaseous dilatation of the more proximal portion of the tract. He confirms Donovan's[22] observation that abdominal roentgenograms without a contrast medium of babies having pyloric stenosis will show stomachs which are large, but not nearly as large as the dilated stomach and duodenal segments seen in duodenal atresia or stenosis. This is an important differential point, for there is no dilated duodenum in patients with pyloric stenosis. Furthermore in pyloric stenosis there is free passage of swallowed air through the entire intestinal tract, whereas in duodenal obstruction distal air will be absent or scanty.

Jejunum and Ileum. The small intestine performs the principal work of digestion and absorption of food. Two main types of motor activity take place in the small bowel, according to Alvarez.[2] The rhythmic segmentations and the probably closely related swaying and pendular movements knead the intestinal contents, mix them with the digestive juices, and spread them again and again over the absorbing surface of the mucous membrane. The other chief type is the peristaltic rush. A wave of contraction travels part way down the bowel, frequently commencing in the duodenum about the time a gastric wave reaches the pylorus. A separate though related phenomenon is the pushing forward of a column of intestinal contents which is usually though not invariably associated with a peristaltic wave of the muscle wall. In addition there are a number of other minor types of small intestinal movements, such as tonus waves, reverse waves, and systolic contraction of the whole bowel which occurs under adverse conditions as when the circulation is shut off.

Alvarez points out further that the bowel is "polarized," in that waves travel much more easily in one direction than another. It is not inert and passive like a hose. When water is injected into the caudal end of the gut it will go only a short distance and then will be pushed back again. There are so many neurologic and muscular mechanisms at work that the mode of progress of solids and liquids through the small bowel can probably never be summed up by any such short phrase as the so-called myenteric reflex or "law of the intestine" of Bayliss and Starling.[5]

In childhood it is not easy to distinguish jejunum from ileum by Roentgen ray appearances. The characteristic prominent jejunal folds when seen are helpful diagnostic aids, but often they fail to become evident. Zwerling and Nelson[124] reported on the roentgenologic patterns of the small intestine in infants and children. They studied 77 subjects ranging in age from 3 months to 11 years, all but 1 in good nutritional condition. Wide variations in appearances were observed at all ages following test meals of 1 to 2 ounces of a barium-water mixture. Only 5, including a 5 year old boy with nutritional deficiency, had the appearance considered as "adult normal." With these 5 children, of whom the youngest was 11 months old, the barium moved in a regular continuous stream with even powdery flocculation of the markings and no marked variations in caliber except in areas of active peristalsis. On the other hand, 38 of the infants and children exhibited coarsening or obliteration of the mucosal markings, with segmentation and irregular flocculations. This latter so-called "infantile" pattern was very similar to the "deficiency" patterns described by Mackie[64] and Golden[33] for adults. The remainder of the group had patterns transitional between the above two types. Zwerling and Nelson concluded that there was no specific age at which the "infantile" changed to the "adult" type of pattern, and that the roentgenologic appearance of the small intestine is not at the present time a reliable criterion for the diagnosis of nutritional deficiency states in childhood.

The above findings are to some extent in conflict with the experience of May and McCreary.[71] In celiac disease (30 patients) and fibrosis of the pancreas (2 cases) they encountered slowing of the segmenting movements and dilatation in the small intestine. Low blood sugar curves secured in the oral glucose tolerance test with these patients were ascribed to defective glucose absorption as a result of sluggish gastro-intestinal motility. When the glucose was given by duodenal tube, to avoid delay in emptying of the stomach, and when active segmenting motion was stimulated in the small intestine by mecholyl, a normal rise in the blood sugar curve was "invariably" obtained. At the same time the clumping disappeared from the gastro-intestinal roentgenograms.

Macy, Reynolds *et al.*[65] have reported on a small series of normal healthy children with various test meals. In all instances, major peristaltic waves were visible in the small intestine only when it was somewhat overloaded with a mass of food. Milk evoked more pronounced wave patterns than did water, though rate of onward movement was slower. When the food approached the region of the ileocecal valve, the intestinal movements were much less active and there was considerable overlapping of the shadows. During the roentgenoscopic observations a sudden propulsion of the contents of the last few inches of the ileum into the cecum was frequently seen. With the different meals it was noted that the children with the most rapid gastric emptying had the least rapid intestinal motility and *vice versa*.

From an analysis of serial Roentgen ray films of 133 infants, aged 1 week

to 6 months, Bouslog *et al.*[11] reported the jejunum rarely visualized with barium. When seen, the jejunum did not present the "feathery" appearance of the adult type. Instead, it appeared sometimes as small isolated masses of barium and other times as a thin continuous line. Occasionally the separated globules were fuzzy in contrast to more clearly cut masses in the ileum. In the ileum the globules arranged themselves more or less isolated from each other, or grouped in masses in the lower right or left quadrant. They frequently remained in the ileum for as long as 5 hours.

In the newly born, according to Henderson,[44] the jejunum and ileum when first filled appeared as continuous well-filled loops. After 3 to 4 hours they became segmented, and segmentation usually increased as the examination progressed. The head of the meal reached the cecum in 3 to 6 hours after the meal has been taken. The terminal ileum was often obscured by segmentation in the distal small intestine.

How long does it take for food to pass through the small intestine, from pylorus to cecum? It is not easy to extract answers to this question from the published reports. The great difficulty lies not so much in lack of interest—though specific attention has frequently not been paid to this topic—as in interpreting the overlapping mixture of shadows resulting from the intermittent discharge of food contents into the intestinal lumen. Following is a series of short statements summarizing data from the reports discussed elsewhere in this paper.

Macy *et al.*[65] reported on the variations in what was termed "jejunal emptying time" exhibited by 7 normal children aged 6 to 10 years, though without giving their criteria for distinguishing jejunum from ileum. With a water-barium meal the time ranged from 1.3 to 3 hours; with milk and barium, 2 to 4.5 hours. When the same test was repeated 18 months later with the milk meal, the range was from 1 to 4 hours, wide differences in responses to the 2 tests were exhibited by several children.

Buchheim[12] fed applesauce containing barium to 23 children aged 1 to 14 years. The stomach emptying time ranged from 1 to 3 hours, average 2 hours. The cecum began to show in 1 to 2 hours, though with 1 child, aged 4, it was outlined by 20 minutes. As a rule the small intestines were completely empty in 2 to 4 hours, but in a few instances the passage took up to 6 hours. With Zwerling and Nelson's[124] 77 children 3 months to 11 years of age who received 1 to 2 ounces of a barium-water mixture the material reached the terminal ileum or cecum in $1\frac{1}{2}$ to 6 hours after being taken.

With infants under 6 months of age receiving a milk-barium meal Bouslog, Cunningham *et al.*[11] noted that the cecum often showed partial filling 3 hours after feeding. By 5 hours it was usually well filled. In this series of cases the films taken immediately after completion of the barium meal showed some food already in the small intestine in 244 out of 281 examinations.

In a small bowel study on 50 newborn infants, Henderson[44] found that the time required for a barium sulfate water meal to enter the cecum ranged from 2 to 6 hours. For 31 of these the times were grouped between 3 and 4 hours.

For adults the time for progress through the small intestine is about the same as that for older children, perhaps a little longer. Under normal circumstances with a milk test meal the first masses of barium reach the cecum as early as 2 hours.[107] By 8 hours most of the food will have passed the ileocecal sphincter, though in some individuals with hyperactivity the ileum may have become empty by 4 hours. With 124 sub-

jects given a water-barium feeding David[19] found onset of cecal filling to spread from less than 2 hours to more than 4 hours; ileal emptying ranged from less than 2 hours to beyond 6½ hours.

The reader should remember that barium sulfate when mixed with a test meal accelerates the rate of passage. This effect has been demonstrated to take place both in the small and large intestines.[2] Consequently, caution must be used in drawing conclusions from comparisons in rates of passage of barium-containing meals, inasmuch as the presence of barium renders all observations abnormal.

Gas in the Small Intestine. As described earlier some of the air which accumulates in the stomach during eating is eliminated by eructation, and the remainder is passed through into the intestinal tract. Paine and Nessa[81] took roentgenograms of 46 normal children from the neonatal period up to 10 years of age to determine how patterns of air in the small bowel change with growth. Gas was found distributed about equally between the small bowel and the colon up to 18 months of age. From 18 months to 6 years relatively large accumulations were massed in the colon with less and less in the small bowel. After 7 years, as with adults, no gas was visualized in the small bowel. However, the number of children studied who were over 4 years of age was too small for this stated upper age limit to be construed exactly.

It is well known among roentgenologists that normally gas cannot be visualized in the small intestine in adult life. One assumes that the wall of the adult small bowel possesses greater tonicity and when inactive stays in a state of more complete contraction or collapse than does that of the child. When the adult small intestine contains gas accumulations, one must suspect the presence of ileus, obstruction or nutritional deficiency.[80]

Soveri[101] forced 200 to 300 cc. of air into the stomach of infants by stomach tube, and followed its passage through the gastro-intestinal tract by Roentgen ray. When the small intestine was empty, air introduced into the stomach passed all the way through in 1 to 2 hours. Deducting ½ hour for evacuation from the stomach, one obtains ½ to 1½ hours as the transit time for small intestinal passage. When air was introduced into the stomach within 3 hours after a regular meal its transit through the small intestine took place more slowly, though with greater rapidity than for the meal itself. Soveri noted that when babies were handled or moved about spontaneously the passage time was accelerated.

Magnusson[69] had found that air introduced under experimental conditions into the adult small intestine can pass all the way through in 10 minutes. The entire adult gastro-intestinal tract can become distended with air within ½ hour.

Snow[99] investigated the importance of position as a factor in the Roentgen ray appearances of intestinal gas in infancy. He found that large accumulations of gas would clear away if babies were kept in a semi-inclined bassinet or lying prone or on the right side rather than in the more customary supine position. Snow ascribed the tendency of infantile colic to cease at about 3 months of age to the spontaneous rolling about in bed that babies begin to do at that age. Many clinics place children scheduled for intravenous urography upon the abdomen for the preceding 12 to 24 hours, in order to cut to a minimum the obscuring network of intestinal gas shadows.

Colon. Food residues are constantly flowing through the ileocecal sphincter into the cecum where mixing of old and new food residues takes place. One of the main functions of the colon is to conserve the water

supply of the body. It is a sluggish organ with slow movements. As Alvarez[2] describes it, much of the progress of its contents is achieved by pressure exerted by new material coming in from above. A few times a day "mass movements" carry material from the transverse colon over into the sigmoid region. During the defecation act the ascending colon assumes an almost globular form; then peristaltic contractions push material from cecum and ascending colon into the transverse colon. About the same time material in the descending colon moves into the rectum. The desire to empty the bowel probably comes when fecal material descends in this way.

The colon of the healthy newborn was reported on by Henderson and Briant[45] in an analysis of the findings in 105 infants aged 2 to 8 days. Fluoroscopy and Roentgen ray of barium enemas were made. Two to 2½ ounces of barium mixture completely filled the colon. Irritability of the large bowel following injection of barium was probably not more marked than in the adult. The mucosal contours rarely showed any defect; any found were believed due to adherent meconium or feces. Haustrations were nearly always present, but were more shallow and less numerous than in older infants and adults. Nineteen of the original group of 105 infants returned at ages varying from 3 months to 1 year for follow-up study. Redundancy of the descending and ascending colon and of the splenic and hepatic flexures was less marked in this older group, evidently due to longitudinal body growth.

With infants in the first year, after a milk-barium meal, Bouslog *et al.*[11] observed that the colon was empty in but 9 out of 281 examinations at 8 hours. At 24 hours in 170, or 61%, the colon was found entirely empty, indicating complete evacuation of the contents. Haustrations were seen sometimes, though not prominent. Some of the infants had spasm, involving the entire colon or but a segment. Peristaltic waves apparently moved the contents with ease. Barium meals were often cut into widely separated segments. Reynolds, Macy *et al.*[89] make no comment as to differences in activity between the child's colon and that of adults.

A moment's reflection makes it evident that the great variations in colon emptying time are tied up in large part with defecation habits. When an individual has been accustomed to performing bowel movements on a regular schedule, the hour of habitual evacuation will exert a significant influence upon the length of time required for a given meal to be passed from the colon, depending upon the hour of day the meal was taken.

Air in the Colon. Gas received in the colon from the small intestine seems to be absorbed by the mucosa or to leak out slowly and soundlessly. Audible passage of flatus occurs frequently in infants, though the quantity passed per day is a negligible fraction of the quantity swallowed. In the newborn under normal circumstances the entire gastro-intestinal tract from stomach to rectum may contain significant accumulations of air within the first 4 hours postpartum.[81]

Wangensteen and Rice[114] discovered that imperforate anus in the newborn can be distinguished from rectal atresia by taking a flat Roentgen ray film of the abdomen with the infant held in the inverted posture and the anal dimple marked with a radio-opaque rod. The gas bubble will outline the distal loop of bowel at the site of the congenital obstruction. By noting the distance between the bowel and the external marker the surgeon will receive invaluable information as to the length of the defective segment of bowel and be guided as to the type of operation needed. In 1 of their cases the gap was very slight at 24 hours, though at 14 hours

the terminal end of the colon gas bubble had been far removed from the anal dimple. Consequently in doubtful cases or those poorly distended it is wise to wait 1 to 2 days before deciding on the length of the segment of atretic bowel between sigmoid and anus.

Spasm of the Colon. Spasm of the large bowel during infancy and childhood is usually accompanied by distressing symptoms among which anorexia, abdominal pain and attacks of nausea are the most prominent.[9] Production or flare-up of symptoms can result from upper respiratory infections,[85] allergy,[29,94] faulty autonomic regulation,[55] pathologic conditions of the abdomen such as diseased appendix,[87] and toxic irritants[9] or as a sequel of bacillary or amebic dysentery.[9] Constipation is the more usual symptom,[9] though Rubin[94] encountered infants under 2 months of age allergic to cow's milk who exhibited loose diarrheal stools containing mucus and blood. Fries and Zizmor[29] were able to corroborate that the colon in allergic patients responds directly to local presence of the allergen. They administered barium enemas containing a small quantity of the known offending allergen to 9 children subject to gastro-intestinal allergic disturbances. In response to these enemas, 5 of the 9 developed colon spasm as evidenced by abdominal cramps and narrowing of all or parts of the colon with prominent haustra and deep sulci. Control allergen-free enemas with these children gave normal roentgenographic contours, without spasm.

Number of Defecations per Day. The number of defecations per day is known to be higher with infants than with older children; but the Reviewer is not familiar with any broad survey of the behavior pattern of this activity in normal children covering increases in age. That the newborn has a bowel evacuation after nearly every feeding is common experience, but the figure for most babies soon falls to 2 to 3 movements daily, and older children have movements once or twice daily. However, as was brought out in a Round Table Discussion of the American Academy of Pediatrics[93] a few years ago, the consensus now holds that a bowel movement daily is not essential for health, even in infancy, provided the baby is comfortable and free from obvious symptoms of distress.

For a small group of 9 children aged 5 to 8 years used by Shepherd, Hummel and Macy[96a] in a study on alimentary tract functioning on diets containing added raw apples or banana, the mean laxation rate over a 30 to 55 day preëxperimental control period was 1.5 bowel movements per day; during the 20 to 40 day experimental period the mean rate was 1.7 per day.

For a summary of average rates of defecation during infancy, the Reviewer has tabulated (Table 1) data collected in the course of two different infant feeding studies performed on identical groups of Philadelphia children in successive years.[119,120] Note that the grand mean laxation rate falls slowly as age in months increases. Figures for the first 2 weeks of life have not been included because the number of infants studied at this age was too small for statistical validity.

Total Gastro-intestinal Transit Time. The period required for foods to pass through the alimentary tract of the infant was studied by Lesné, Binet and Paulin.[61] Carmine in 0.2 gr. quantities, dissolved in water, was fed and the stools observed for the appearance and later fading away of this pigment:

Age	1 to 3 mos.	3 to 6 mos.	6 mos. to 1 yr.	1 to 2 yr.
No. of infants . . .	35	22	15	12
Appearance time . .	8 hr. 30 min.	8 hr. 40 min.	9 hr. 20 min.	10 hr.
Disappearance time .	18 hr. 40 min.	19 hr. 50 min.	20 hr. 40 min.	23 hr.

These figures, representing averages presumably, demonstrate that the rate of passage becomes slower with increasing age, reflecting the growing length of and greater control over the colon. Breast milk passes through a little more quickly, probably because it is lower in residue:

	No.	Appearance in stool (average)	Disappearance in stool (average)
Breast-fed infants	30	8 hr. 25 min.	17 hr. 30 min.
Mixed breast and bottle feedings	40	8 hr. 55 min.	19 hr. 30 min.
Artificially fed infants	51	9 hr. 50 min.	20 hr. 50 min.

Variations from 4 to 12 hours were observed in first appearance time for the same breast-fed baby and from 3 to 20 hours for the same artificially fed baby, illustrating the great irregularities and spontaneous fluctuations which are normal physiologic occurrences.

TABLE 1.—LAXATION RATE OF NORMAL INFANTS IN RELATION TO AGE IN MONTHS

Milk	No. of infants†	Age in months 1‡	2	3	4	5	6	7	8	9	10	11	12
1*	68	3.53	3.13	2.62	2.48	2.43	2.40	2.44	2.28	2.45			
2*	58	2.65	2.50	2.22	2.09	2.21	2.17	2.18	2.03	1.84			
3*	58	2.70	2.53	2.42	2.20	2.18	2.32	2.18	2.23	2.16			
4*	65	2.55	2.38	2.16	2.09	2.22	2.16	2.20	2.05	2.00			
5*	237	2.58	2.91	3.00	2.93	2.50	2.58	2.27	2.04	1.87	2.08	1.89	1.84
6*	173	3.00	3.11	2.79	2.89	2.69	2.48	3.13	2.07	1.94	1.98	1.87	1.79
7*	234	2.31	2.19	1.85	1.90	1.86	1.88	1.69	1.41	1.59	1.32	1.40	
8*	199	2.26	2.35	2.28	2.34	2.16	2.20	2.21	2.08	1.92	1.90	1.83	1.54
Mean		**2.67**	**2.63**	**2.41**	**2.37**	**2.28**	**2.27**	**2.29**	**2.02**	**1.97**	**1.82**	**1.75**	**1.72**

* No. 1, A vitamin-fortified iron-containing modified milk mixture containing 7.4% lactose 2.8% butter fat and 65 to 85 units of thiamine; No. 2, same as No. 1, but with 6.6% lactose, 2.4% butter fat and 1.6% corn syrup; No. 3, same as No. 2, but with 8.2% lactose, no corn syrup and 35 to 55 units of thiamine; No. 4, same as No. 3, but with 65 to 85 units of thiamine; No. 5, pasteurized market milk, with 4 to 4.2% butter fat, boiled for 5 minutes in home; No. 6, same as No. 5, but sonic homogenized and fed unboiled; No. 7, same as No. 5, homogenized at low pressure and fed unboiled; No. 8, same as No. 5, homogenized at high pressure (2500 pounds) and fed unboiled.
† Not every infant was followed for the full period of observation.
‡ Infants aged 3 and 4 weeks only.

Kahn[52] studied the duration of alimentary tract passage in 30 healthy infants aged up to 16 months in a total of 200 determinations. Normal feedings were given marked with charcoal or carmine. Striking variations in transit time were detected, not related to the age in months. The times ranged from 4 to 20 hours, the mean being about 15 hours.

It was found that when the markers were introduced into different meals throughout the day that the 5 A.M. feeding came through in a mean time of 12 hours, the 1 P.M. feeding in a mean time of 19 hours, and the 9 P.M. feeding in a mean time of 15 hours.

When passage of breast milk was compared with that of artificial formula made of cow's milk, the author stated that breast milk passed more rapidly, though calculation of his published data for infants within the age period in which breast milk was given revealed no significant difference in the mean transit times.

When 2 successive meals were marked with carmine and charcoal respectively, some mixing of the pigments would be apparent in the stools. If, however, there was a wait of 12 hours between the marked meals the pigment in the feces was no longer mixed. It is apparent that individual stools do not necessarily bear any specific relation to individual meals. Interestingly in 1 child passage of 1 marked meal took 66 hours; when repeated, but 23½ hours.

Using the Roentgen ray and barium to study meal passage, Kahn[52] found that the longest period for the stomach emptying was 4 to 5 hours, for the small intestine 7 to 8 hours, for the large intestine 20 to 24 hours. Thus

the differences in speed of passage existing between adults and infants lies almost entirely in the greater rate of movements through the colon. The usual time required by the healthy adult is 24 to 48 hours.

With 13 premature babies weighing 1450 to 2870 gm. at the time of the test and ranging from 2 days to 5 months of age, the duration of passage varied from 6 to 19 hours, apart from 1 instance in which the marker took 42 hours to come through. The mean transit time was 13 hours. Thus there was less variation than with full-term infants.

With 23 infants having dyspepsia and frequent mucus-containing stools the total transit time was 6 to 10 hours. Roentgen ray studies showed the passage through the small intestine to be much more rapid than normal. Gastric emptying time was not accelerated, lasting 3 to 4½ hours, but the small intestine was usually empty by 3½ hours later, and the large bowel had evacuated in 2 to 5 hours. When dyspeptic infants had slower transit times the delay was due to more sluggish evacuation of the rectum.

In chronic disease, as is well known, intestinal and abdominal wall atony and slower transport of food may develop. This principle is illustrated in Strickler, Fisher and Lowenberg's[103] study of chronic eczema. Twenty-eight children aged 15 months to 11 years having chronic eczema of diverse types and 5 normal controls aged 18 months to 8 years were studied with a barium meal. The first film taken at 6 hours showed barium residue still in the stomach in 12 of the eczema patients, and in but a single control. As for elimination from the rectum, 3 of the controls were rid of the barium by 24 hours, and the other 2 by 48 hours. In the eczema group, however, 15 still had retention at 96 hours, and took up to 6 days longer for elimination; 1 went 18 days before excreting all the barium. Many of these passed regular bowel movements during the time the opaque meal was stalled in the colon.

Comparison of Motility in Child and Adult. Wasson[116] compared in general terms the motility of the gastro-intestinal tract in infant and child with that in the adult. In the infant food is transported as a steady current through stomach, small intestine and colon without any pause save in the stomach which functions as a reservoir. In the adult the stomach and small intestine empty in approximately the same time interval as in the infant and young child. However, a great delay occurs in the colon which may require 24 to 48 hours longer to empty than the infant colon. This slowing of the colon begins soon after infancy; at a few years of age the colon emptying time may approximate that of the adult. As an individual grows up his sphincters become more vigorous in their action, the contractions of stomach and intestine grow stronger, and localized changes and enlargements develop. Among other changes, the jejunal loops lose their irregular globular pattern and assume the snow-flake appearance of the adult. The outline of the colon too becomes much sharper, with more complete filling and development of the haustral markings. Wasson concluded that the slower rate of evacuation of the adult colon is due to more powerful sphincter control and differently coördinated reflexes.

U. S. P. H. S. Hospital, Sheepshead Bay,
Brooklyn 24, N. Y.

REFERENCES

(1.) **Aimé, P.**, and **Lelong, M.**: J. de radiol. et d'electrol., **18**, 466, 1934. (2.) **Alvarez, W. C.**: An Introduction to Gastro-Enterology, New York, Hoeber, 1940.
(3.) **Barbour, O.**: J. Am. Med. Assn., **97**, 455, 1931. (4.) **Bau, A.**: Kinderärztl. Praxis, **8**, 277, 1937. (5.) **Bayliss, W. M.**: Principles of General Physiology, 4th ed.,

London, Longmans Green, 1924. (6.) **Benassi, E.**: Radiol. Med., **17**, 1334, 1930. (7.) **Bexelius, G.**: Acta Pædiat., **25**, 22, 1939. (8.) **Birnberg, T. L.**: Am. J. Dis. Child., **38**, 1183, 1929. (9.) **Bloom, C. J.**: New Orleans Med. and Surg. J., **94**, 322, 1942. (10.) **Bouslog, J. S.**: Radiology, **28**, 683, 1937. (11.) **Bouslog, T. S., Cunningham, T. D., Hanner, J. P., Walton, J. B.,** and **Waltz, H. D.**: J. Pediat., **6**, 234, 1935. (12.) **Buchheim, I.**: Arch. f. Kinderheilk., **72**, 50, 100, 1923.

(13.) **Calvin, J. K.,** and **Denenholz, E. J.**: Arch. Pediat., **58**, 26, 1941. (14.) **Cautley, E.,** and **Bent, C. T.**: Lancet, **168**, 1679, 1902. (15.) **Casparis, H.**: Ann. Int. Med., **7**, 625, 1933. (16.) **Christensen, O.,** and **Schultz, A. L.**: Acta med. Scandinav., **81**, 325, 1934. (17.) **Clark, G. A.**: Proc. Physiol. Soc., J. Physiol., **54**, lix, 1920. (18.) **Cohen, P.**: Am. J. Dis. Child., **61**, 135, 1941.

(19.) **David, O.**: Mitt. a. d. Grenzgeb. d. Med. u. Chir., **31**, 209, 1918. (20.) **Demuth, F.**: Ergebn. d. inn. Med. u. Kinderh., **29**, 90, 1926. (21.) **Dietrich, A.**: Ztschr. f. Kinderh., **50**, 705, 1931. (22.) **Donovan, E. J.**: Am. J. Surg., **39**, 377, 1938.

(23.) **Faber, H. K.,** and **Davis, J. H.**: J. Am. Med. Assn., **114**, 847, 1940. (24.) **Findlay, L.**: Arch. Dis. Child., **13**, 145, 1938. (25.) **Flesch, H.,** and **Péteri, I.**: Ztschr. f. Kinderh., **2**, 263, 1911. (26.) **Foote, J.**: Am. J. Dis. Child., **15**, 351, 1918. (27.) **Ford, N., Brown, A.,** and **McCreary, J. F.**: Am. J. Dis. Child., **61**, 41, 1941. (28.) **Freudenberg, E.**: Physiologie und Pathologie der Verdauung im Sauglingsalter, Berlin, Springer, 1929. (29.) **Fries, J. H.,** and **Zinmor, J.**: Am. J. Dis. Child., **54**, 1939, 1937. (30.) **Frollo, G.**: (*a*) Pediatria, **46**, 806, 1938; (*b*) Ibid., **47**, 31, 782, 1939.

(31.) **Gefferth, K.**: Arch. f. Kinderh., **103**, 231, 1934. (32.) **Glanzmann, E.**: Kinderärztl, Praxis, **4**, 453, 1933. (33.) **Golden, R.**: Radiology, **36**, 262, 1941. (34.) **Gray, J. S., Bradley, W. B.,** and **Ivy, A. C.**: Am. J. Physiol., **118**, 463, 1937. (35.) **Grenet, H., Gautheron** and **Aupinel**: Bull. Soc. pediat. de Paris, **37**, 547, 1940.

(36.) **Haas, S. V.**: J. Mt. Sinai Hosp., **7**, 411, 1940–41. (37.) **Hadary, G., Sommer, H. H.,** and **Gonce, J. E., Jr.**: J. Dairy Sci., **26**, 259, 1943. (38.) **Hainiss, E.,** and **Surányi, J.**: Arch. f. Kinderh., **100**, 219, 1936. (39.) **Halbertsma, T.**: (*a*) Maandschr. v. Kindergeneesk., **5**, 24, 1935; (*b*) Acta Pædiat., **18**, 463, 1935–36. (40.) **Harnapp, G. O.**: Jahrb. f. Kinderh., **140**, 31, 1933. (41.) **Hasse, C.**: Arch. f. Anat. u. Physiol., Anat. Abt., p. 321, 1905. (42.) **Hawk, P. B., Rehfuss, M. E.,** and **Bergeim, O.**: Am. J. Med. Sci., **171**, 359, 1926. (43.) **Hellebrandt, F. A.,** and **Tepper, R. H.**: Am. J. Physiol., **107**. 355, 1934. (44.) **Henderson, S. G.**: Am. J. Roentgenol. and Rad. Ther., **48**, 302, 1942, (45.) **Henderson, S. G.,** and **Briant, W. W.**: Radiology, **39**, 261, 1942. (46.) **Herrin, R. C.**: Am. J. Physiol., **115**, 104, 1936. (47.) **Hofmann, E.,** and **Peiper, A.**: (*a*) Klin. Wchnschr., **14**, 1723, 1935; (*b*) Monatschr. f. Kinderh., **70**, 54, 1937. (48.) **Hurst, A.**: J. Laryngol. and Otol., **58**, 60, 1943.

(49.) **Ivy, A. C.,** and **Fauley, G. B.**: Am. J. Physiol., **91**, 206, 1929.

(50.) **Jackson, C.,** and **Jackson, C. L.**: Bronchoscopy, Esophagoscopy and Gastroscopy, Philadelphia, Saunders, 1934. (51.) **Jochims, J.**: Ztschr. f. Kinderh., **58**, 796, 1937.

(52.) **Kahn, W.**: Ztschr. f. Kinderh., **29**, 321, 1921; **33**, 55, 1922. (53.) **Kantor, J. L.,** and **Marks, J. A.**: Ann. Int. Med., **3**, 403, 1929. (54.) **Kasahara, M.**: Am. J. Dis. Child., **12**, 73, 1916. (55.) **Kerley, C. G.**: J. Am. Med. Assn., **99**, 1062, 1932. (56.) **Kerley, C. G.,** and **Le Wald, T.**: Digestive Disturbances in Infants and Children, Annals of Roentgenology, New York, Hoeber, vol. 3, 1923. (57.) **Knight, G. C.**: Brit. J. Surg., **22**, 155, 1934. (58.) **Krüger, W.**: Monatschr. f. Kinderh., **21**, 257, 1921.

(59.) **Lelong, M.,** and **Aimé, P.**: Bull. Soc. de pediat. de Paris, **33**, 230, 1935. (60.) **Lereboullet, P., Lelong, M.,** and **Aimé, P.**: Presse méd., **43**, 154, 1935. (61.) **Lesné, E., Binet, L.,** and **Paulin, A.**: Arch. de med. d. enfants, **23**, 449, 1920. (62.) **Levesque, J.,** and **Perrot, R.**: Bull. Soc. pédiat. de Paris, **57**, 587, 1940.

(63.) **Mackay, H. M. M.**: Arch. Dis. Child., **16**, 1, 1941. (64.) **Mackie, T. T.**: J. Am. Med. Assn., **117**, 910, 1941. (65.) **Macy, I. G., Reynolds, L., Souders, H. J.,** and **Olson, M. B.**: Am. J. Roentgenol., **43**, 394, 1940. (66.) **Macy, I. G., Reynolds, L.,** and **Souders, H. J.**: Am. J. Physiol., **126**, 75, 1939. (67.) **Magliano, H.,** and **Hansen, E.**: Arch. Am. de méd., **13**, 18, 1937. (68.) **Magnusson, W.,** and **Engström, H.**: Acta Pædiat., **13**, 348, 1932. (69.) **Magnusson, W.**: Acta Radiol., **12**, 552, 1931. (70.) **Marfan, A. B.**: Nourrisson, **24**, 17, 1936. (71.) **May, C. D.,** and **McCreary, J. F.**: J. Pediat., **17**, 143, 1940. (71*a*.) **May, C. D., McCreary, J. F.,** and **Blackfan, K. D.**: J. Pediat., **21**, 289, 1942. (72.) **McCann, J. C.**: Am. J. Physiol., **89**, 497, 1929. (73.) **McIntosh, R.,** and **Donovan, E. J.**: Am. J. Dis. Child., **57**, 116, 1939. (74.) **Meuwissen, T.,** and **Sloof, J.**: (*a*) Maandschr. v. Kindergeneesk., **1**, 107, 1931; (*b*) Acta Pædiat., 1932; (*c*) Am. J. Dis. Child., **48**, 1304, 1934. (75.) **Mosher, H. P.**: J. Laryngol. and Otol., **45**, 161, 1930. (76.) **Myerson, A.** and **Ritvo, M.**: J. Am. Med. Assn., **107**, 24, 1936.

(77.) **Negus, V. E.**: (*a*) J. Laryngol., and Otol., **40**, 702, 1925; (*b*) Ibid., **51**, 100, 1936; (*c*) Ibid., **58**, 46, 1943. (78.) **Nicholson, P.**: J. Pediat., **9**, 647, 1936. (79.) **Northup, D. W.,** and **Van Liere, E. J.**: J. Pharmacol., **70**, 297, 1940.

(80.) **Paine, J. R.**: Am. J. Surg., **61**, 87, 1942. (81.) **Paine, J. R.**, and **Nessa, C. B.**: Surgery, **11**, 281, 1942. (82.) **Parmalee, A. H.**: in Brennemann, J., System of Pediatrics, Hagerstown, Md., Prior, **3**, 5, 15. (83.) **Pasette, S. E.**: Arch. Pediat., **50**, 279, 1933. (84.) **Pearcy, J. F.**, and **Van Liere, E. J.**: Am. J. Physiol., **78**, 64, 1926. (85.) **Peiper, A.**, and **Isbert, H.**: Jahrb. f. Kinderh., **120**, 48, 306, 312, 1928. (86.) **Peiper, A.**: (*a*) Monatschr. f. Kinderh., **50**, 20, 1931; (*b*) Ibid., **63**, 39, 1935; (*c*) Ergebn. d. inn. Med. u. Kinderh., **50**, 527, 1936; (*d*) Arch. f. d. ges. physiol., **242**, 751, 1939. (87.) **Pfaundler, M. V.**: Blatt. f. Sauglingsfors., **8**, 33, 1916.

(88.) **Quigley, J. P.**: Am. J. Digest. Dis., **10**, 418, 1943.

(89.) **Reynolds, L., Macy, I. G., Hunscher, J.**, and **Olson, M. B.**: Am. J. Roentgenol., **43**, 517, 1940. (90.) **Reynolds, L., Macy, I. G.**, and **Souders, J. J.**: J. Pediat., **15**, 1, 1939. (91.) **Rogatz, J. L.**: Am. J. Dis. Child., **28**, 53, 69, 582, 1924. (92.) **Robertson, D. E.**: Ann. Surg., **112**, 687, 1940. (93.) Round Table on Infant Feeding Including Constipation and Colic, J. Pediat., **16**, 119, 1940. (94.) **Rubin, M. I.**: Am. J. Med. Sci., **200**, 385, 1940. (95.) **Runström, G.**, and **Wallgren, A.**: Acta Pædiat., **17** (Suppl. 1), 261, 1934.

(96.) **Shay, H.**, and **Gershon-Cohen, J.**: Am. J. Digest. Dis., **2**, 608, 1936. (96*a*.) **Shepherd, M. L., Hummel, F. C.**, *et al.*: Am. J. Digest. Dis., **7**, 248, 1940. (97.) **Sleeth, C. K.**, and **Van Liere, E. J.**: Am. J. Physiol., **118**, 272, 1937. (98.) **Smith, C. H.**, and **Le Wald, L. T.**: Am. J. Dis. Child., **9**, 261, 1915. (99.) **Snow, W.**: Am. J. Roentgenol., **38**, 779, 1937. (100.) **Solis-Cohen, L.**, and **Bruck, S.**: Radiology, **23**, 173, 1934. (101.) **Soveri, V.**: Acta Pædiat. (Suppl. 3), **23**, 1, 1939. (102.) **Steinko, R.**: Monatschr. f. Kinderh., **26**, 166, 1923. (103.) **Strickler, A., Fisher, M. K.**, and **Lowenberg, H.**: Arch. Pediat., **53**, 397, 1936.

(104.) **Tallerman, K. H.**: Proc. Roy. Soc. Med., **28**, 411, 1935. (105.) **Thomas, J. E.**: Gastroenterology, **2**, 32, 1935. (106.) **Theile, P.**: Ztschr. f. Kinderh., **15**, 318, 1917. (107.) **Todd, T. W.**, and **Kuenzel, W. M.**: (*a*) J. Lab. and Clin. Med., **14**, 1017, 1929; (*b*) Ibid., **15**, 143, 1929; (*c*) J. Comp. Psych., **10**, 167, 1930. (108.) **Tyson, R. M.**: Arch. Pediat., **43**, 818, 1926.

(109.) **Van der Bogert, F.**: Arch. Pediat., **50**, 585, 1933. (109*a*.) **Virasoro, J. E.**: Prensa méd. argent., **22**, 793, 1935. (110.) **Van Liere, E. J., Sleeth, C. K.**, and **Northup, D. W.**: (*a*) Am. J. Physiol., **119**, 480, 1937; (*b*) Am. J. Digest. Dis. and Nutr., **5**, 18, 1938. (111.) **Van Liere, E. J.**, and **Northup, D. W.**: (*a*) Am. J. Digest. Dis., **8**, 26, 1941; (*b*) Gastroenterology, **1**, 279, 1943. (112.) **Vertue, H. S. H.**: Arch. Dis. Child., **14**, 173, 1939.

(113.) **Wallgren, A.**: Arch. Dis. Child., **15**, 103, 1940. (114.) **Wangensteen, O. H.**, and **Rice, C. C.**: Am. J. Surg., **92**, 77, 1930. (115.) **Wangensteen, O. H.**, and **Rea, C. E.**: Surgery, **5**, 327, 1939. (116.) **Wasson, W. W.**: Radiology, **37**, 277, 1941. (117.) **Werle, J. M.**: Am. J. Physiol., **131**, 606, 1941. (118.) **Wieland, E.**: Kinderärztl. Praxis, **10**, 149, 1939. (119.) **Wolman, I. J.**, and **Borowsky, S.**: Am. J. Dis. Child., **65**, 827, 1943. (120.) **Wolman, I. J., Borowsky, S., Nicholas, R.**, and **Spur, B.**: J. Pediat., **21**, 45, 1942. (121.) **Wolman, I. J.**: Am. J. Med. Sci., **206**, 770, 1943. (122.) **Wright, C. B.**: Arch. Int. Med., **33**, 435, 1924.

(123.) **Ylppö, A.**: Acta. Pædiat., **24**, 258, 1939.

(124.) **Zwerling, H.**, and **Nelson, W. E.**: Radiology, **40**, 277, 1943.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

FRANK B. BLOCK, M.D.

SURGEON, JEWISH HOSPITAL, PHILADELPHIA, PA.

AND

DOUGLAS P. MURPHY, M.D.

ASSISTANT PROFESSOR OF OBSTETRICS AND GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA PHILADELPHIA, PA.

ANALGESIA IN OBSTETRICS

By James F. Donnelly, M.D.

HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

The purpose of this paper is to discuss the drugs which are given during childbirth; to relieve pain, to provide the loss of sensation, or to render the parturient amnesic for the pain. The terms analgesia, anesthesia and

amnesia are used to describe the preceding effects. These terms are used interchangeably in this paper.

Efforts to relieve pain during labor reach far into the past. Ploss and Bartels[31] state that, with the single exception of the American Indian, all races of the past and present have attempted to relieve pain during childbirth. Confirmation of this statement is afforded by the wide variety of pain-relieving devices used by primitive peoples. An equally wide, but more effective variety is in vogue today.

Modern efforts at analgesia were initiated by Simpson in 1847 with ether which he soon replaced with chloroform. An ideal analgesic agent is being sought constantly, but so far in vain. An ideal analgesic should be universally applicable, inexpensive and easily administered. It should have no harmful effect on the mechanism of labor, the mother, or the infant.

The majority of this discussion will be devoted to the two newest analgesics, preceded by brief mention of older and more familiar analgesics.

Morphine and Related Drugs. Morphine and its related compounds have excellent analgesic properties. The use of morphine in obstetrics was popularized by von Steinbuchel in 1902. The analgesia and amnesia obtained were satisfactory, but the fetal and maternal complications were so frequent that it was largely discarded. It is still utilized but it is given only in the early stages of labor. In a recent article Mengert[29] concluded that the greatest fetal respiratory depression occurs during the third hour after the administration of morphine and that it should be avoided in premature labors. He feels that, with careful supervision and with adequate resuscitation facilities, it can be used safely. We use morphine sulfate analgesia frequently at the Hospital of the University of Pennsylvania and feel that it is safe when Mengert's warnings are observed. Although heroin[24] and dilaudid[32] produce less fetal depression they are not widely used.

Barbituric Acid Derivatives. According to Stander,[36] barbituric acid derivatives are the analgesic drugs most commonly used in this country. They do not relieve pain but make the patient amnesic. Of these derivatives, pentobarbital is used most widely. Irving[18] and associates, reporting upon its effectiveness in 1934, concluded that it was nearly ideal. The restlessness associated with pentobarbital amnesia is so great that special nursing care is necessary. Its use is contraindicated, for the same reason, in complications requiring rest, such as in cardiac and pulmonary disease. Recently it has been found to depress the fetal and maternal prothrombin time.[11] This effect can be counteracted by the antepartum administration of vitamin K.

Other Well-known Analgesics. Rectal ether, chloral hydrate and paraldehyde are given less frequently than morphine or the barbiturates in labor. They do not produce amnesia as satisfactorily as do the barbiturates and do not offer any greater safety.

Nitrous oxide, ethylene, ether and chloroform are well-known inhalation analgesic agents and will not be discussed. Two newer analgesic agents, vinethene and cyclopropane are in the process of evaluation. Karp and Richardson[20] have pointed out the many advantages of cyclopropane for obstetrical procedures. It is less irritating to the respiratory tract than most inhalation anesthetics; it provides adequate analgesia and relaxation for the majority of obstetrical operations; it has no deleterious effect on the kidney or liver and, because it is used with a high per cent of oxygen, it does not reduce the oxygen available to the fetus *in utero*. Our own experience with cyclopropane in Cæsarean sections confirms these observations. Very little has been written on the use of vinethene in obstetrics.

Hartmann,[16] in a recent report, regarded it as a safe analgesic agent for delivery. It should not be used in the presence of liver disease or if the delivery will require more than 30 minutes.

The safety of spinal analgesia has been debated since Cosgrove[8] reported its successful use in 1934 for Cæsarean section. Many obstetricians feel that it is unsafe. Two recent reports[2,39] indicate that it is a safe and valuable obstetrical analgesic. They stress the necessity of proper technique and careful observance of the contraindications. Most of the complications with spinal are catastrophic, such as uterine atony with hemorrhage, respiratory failure, intraspinal infections and peripheral vascular collapse. On account of the potential dangers associated with spinal analgesia it can be used only where proper facilities are available.

Completeness demands mention of intravenous analgesia, hypnosis and pudendal nerve block. Although some authors[6,37] think that intravenous analgesia is safe, it is not generally believed to be safe enough for use in obstetrics. Kroger and DeLee[22] reported upon the use of hypnosis to produce analgesia during labor and delivery. They confirmed the observations of others who have used it with success. The low risk to the mother and baby warrant further investigation of this method. No comments need be made on the use of pudendal field block. It is a simple, inexpensive and satisfactory method of relieving perineal pain for delivery. DeLee for years favored more extensive use of this method in his comments in the Yearbooks of Obstetrics and Gynecology. He, likewise, encouraged the use of local infiltration for Cæsarean section.

The use of Demerol and the introduction of continuous caudal analgesia are the two outstanding new developments in obstetrical analgesia.

Demerol. Demerol (ethyl 1-methyl-4-phenylpiperidine-4-carboxylate) is a synthetic drug which can be given orally, intramuscularly, or intravenously. It combines the analgesic properties of morphine and the antispasmodic properties of atropine, although it is unrelated chemically to either of them. The analgesic effect of this substance, determined by a variety of methods, is less than that of morphine, but greater than that of codeine.[3] Its antispasmodic effect on the smooth muscle of the intestinal, urogenital and respiratory tracts has been demonstrated in animals.[9,15] This action is thought to be a direct one on the smooth muscle. It has no effect on the uterine contractions of human beings.[40]

Animal experiments reveal that large doses of Demerol produce excitement, ataxia, spasticity, clonic movements, convulsions and death.[15] Chronic administration of Demerol has led to anorexia and weight loss.[9] Therapeutic doses in man produce side reactions in 25% (Schumann[33]) of the patients receiving the drug by mouth and nausea and vomiting in 29% (Gallen and Prescott[13]). The side reactions include dizziness, flushing, dryness of the mouth, sweating and euphoria. Most of these are transitory.

A few reports have been made upon the use of Demerol in obstetrics. A carefully analyzed series of 1000 deliveries has been reported by Schumann.[33] Satisfactory amnesia was secured by 90% of his patients when the Demerol was accompanied with scopolamine. This degree of success is slightly lower than that obtained with nembutal-scopolamine sedation in 1934 by Irving at the same clinic.[18] It is important to note that the dosage of scopolamine used by Schumann was in the same range as that employed by Kirschbaum,[21] who obtained satisfactory amnesic results with scopolamine alone. Only 60% of the patients treated by Gallen and Prescott[13] had satisfactory analgesia. Compared to patients sedated with other drugs, the patients receiving Demerol had definitely shorter labors.[14]

Schumann found that the average duration of labor under Demerol and scopolamine in primipara was 2.5 hours shorter than under nembutal-scopolamine analgesia, and 1.2 hours shorter in multipara. Gallen and Prescott reported apnea in 10% of the infants and Schumann stated that 15.29% of his infants required resuscitation. The frequency of stillbirths and neonatal deaths was remarkably low in all reports, and no serious maternal complications were noted.

Sympathetic Nerve Block. Sympathetic nerve block, which is the basis of caudal analgesia, is accomplished either by paravertebral or epidural injection. The former method was suggested by Shumacker,[24] and has been studied more intensively since then by Jarvis.[19] Although single injections into the epidural space through the sacral hiatus have been used in this country for years, it remained for Hingson and Edwards[17] to develop a technique in which the analgesic solution could be administered intermittently. Manalan[26] substituted a small nylon catheter for the malleable needle used by the preceding authors. Block and Rochberg[4] later developed a method of administering the solution by continuous drip.

An understanding of the nerve supply of the uterus as described by Cleland[7] is essential to the proper performance of sympathetic nerve block analgesia. Briefly he found that the motor fibers of the uterus are derived from the sympathetic fibers arising in the aortic ganglia, reinforced by ones from the solar, renal and genital ganglia. The sensory nerves of the fundus of the uterus run through the sympathetic chain, entering the spinal cord at the eleventh and twelfth dorsal segments. The sensory innervation of the cervix, and upper portion of the vagina, is derived from the sacral plexus. The sensory and motor supply to the lower vagina, pelvic floor and perineum are derived from the lower lumbar and pelvic somatic nerves.

Epidural block by the serial or continuous caudal technique consists of passing a malleable needle or catheter through the sacral hiatus and injecting an analgesic solution into the epidural space. Metycaine and procaine solutions are used most frequently. The amount of solution injected determines the height at which the block will occur. The needle or catheter is left in place during labor and delivery, and sufficient solution is given to maintain skin anesthesia at the level of the tenth dorsal segment. Skin anesthesia at this level blocks the pain fibers to the fundus of the uterus. For detailed explanation of the various techniques, the reader is referred to the original articles by Hingson and Edwards[10] for serial injection with a malleable needle, Manalan[26] for serial injection with a catheter, Block and Rochberg[4] for the continuous drip technique and Jarvis[19] for the technique of paravertebral block.

Although continuous and serial sympathetic block are relatively new techniques, they have disadvantages as well as advantages. Below is a partial list of the advantages and disadvantages of this method as reported by McCormick.[27]

Advantages. 1. Labor is remarkably free of pain.

2. The patient retains all of her faculties.

3. It is valuable in cardiac and pulmonary complications.

4. In premature labors the relaxation of the pelvic floor combined with the reduction of fetal depression are extremely desirable. (This is considered by McCormick as the most outstanding contribution of caudal anesthesia.)

5. Uterine bleeding in the third stage is lessened.

6. In teaching medical students, it is possible for the student and instructor to do a rectal examination at the same time.

Disadvantages. 1. The procedure requires the constant attendance of someone skilled in its use.

2. It is available to only about 60% of women, those delivered in hospitals. (Subtract from this number a large percentage for those women delivered in hospitals without the necessary facilities for continuous caudal analgesia, 9% for failure to insert the needle, and an uncertain percentage for patients considered unsuitable.)

3. It is contraindicated by placenta prævia, premature separation of the placenta, uterine inertia, disproportion, anemia, drug sensitivity, sacral anomalies, and local infections.

4. There is a possibility of peripheral nerve damage, infection and unrecognized spinal tap.

5. Operative interference is increased.

6. The maternal mortality rate is increased. (Judging from McCormick's discussion of this point, this seems to be the most significant disadvantage.)

Since there is considerable difference of opinion in regard to the desirability of using continuous caudal analgesia, some of the results obtained by different authors are summarized below.

PAIN RELIEF

Reference	*No. of patients*	*Results*
1. Hingson and Edwards[17]	33	Complete relief in all
2. Block and Rochberg[4]	39	Complete relief in all
3. Block and Rotstein[5]	61	Successful insertion of needle in 95%; supplementary anesthesia in 7 patients
4. Siever and Mousel[35]	300	Satisfactory, 288; supplementary anesthesia, 12
5. Lyons and Hansen[25]	200	Satisfactory in 195 patients
6. McCormick[27]	100	Complete success, 40%; partial success, 40%; failed, 20%
7. Lull[23]	553	Complete success, 92%
8. McElroy and Donnelly[28]	200	Failed insertion, 38; complete success, 98; partial success, 64
9. Jarvis[19]	70	No comment

Insertion of the needle into the sacral hiatus sometimes is difficult, if not impossible, even in the hands of experts. Hingson and Edwards report success in only 91% of their cases. The most frequent cause of failure, in our hands, to insert a needle successfully, is obesity which obscures the usual landmarks. Secondly, inexperience leads to more frequent failures. The third most common cause of failure is sacral anomalies, which are said to occur in 10 to 15% of patients.

With the exception of two of the above reports, excellent results were noted. Hingson and Edwards,[17] reporting the results in 10,000 cases from clinics throughout the country, stated that complete relief was obtained in 81%, partial relief in an additional 12% and failure in the remaining 7%. These authors do not state whether this latter figure includes the cases in which it was impossible to insert the needle.

The frequency of operative delivery is increased under serial caudal analgesia on account of the fact that the presenting part does not reach as low a level in the pelvis as usual, since the block inhibits the normal expulsive reflex; and that, in the absence of the usual resistance of the pelvic floor, the normal mechanism of rotation is disturbed.

The application of outlet forceps is a simple procedure and without danger to mother and infant. On the other hand, the applications of forceps high in the pelvis, or requiring rotation of the fetal head are a more serious matter. Therefore, no matter how skilled the obstetrician, the fetal risk will be increased unnecessarily with the use of serial caudal

analgesia, in spite of the marked relaxation of the pelvic floor which facilitates forceps manipulations.

MODE OF DELIVERY

Reference	*No. of patients*	*Results*
1. Hingson and Edwards[10]	33	Spontaneous, 10; operative, 23
2. Block and Rochberg[4]	39	Spontaneous, 10; operative, 29
3. Block and Rotstein[5]	61	"Does not interfere with spontaneous delivery"
4. Siever and Mousel[35]	300	Primiparas—Spontaneous, 30% operative, 70% Multiparas—"Multiparas were able to push the baby out rather easily"
5. Lyons and Hansen[25]	200	"Large percentage of operative deliveries"
6. McCormick[27]	100	"Necessitate increased operative delivery"
7. Lull[23]	553	"Increase in operative delivery" "More posterior positions and particularly transverse arrests" "Breech decomposition and internal podalic version cannot be accomplished"
8. McElroy and Donnelly[28]	200	Spontaneous, 50; operative, 112
9. Jarvis[19]	70	No comment

EFFECT ON THE FETUS

Reference	*No. of patients*	*Results*
1. Hingson and Edwards[10]	33	One stillbirth; all other babies cried immediately
2. Block and Rochberg[4]	39	One stillbirth; no fetal apnea
3. Block and Rotstein[5]	61	Two stillbirths and 1 neonatal death; no apnea
4. Siever and Mousel[35]	300	"All cried spontaneously; fetal mortality, 1%"
5. Lyons and Hansen[25]	200	No comment
6. McCormick[27]	80	Two stillbirths and 3 neonatal deaths, 1 of which is attributed to the analgesia
7. Lull[23]	553	"All cried almost immediately"
8. McElroy and Donnelly[28]	162	Apnea, 21; stillbirths, 1; neonatal deaths, 6
9. Jarvis[19]	70	"All cried and breathed immediately"

There is general agreement that fetal respiratory depression is infrequent under continuous caudal analgesia. It is our impression, likewise, that this is the case. The respiratory depression is less in our hands than that obtained with inhalation anesthesia combined with narcotics or barbiturates; but the rate of fetal apnea of our infants born under morphine analgesia is only 0.7% more.

THIRD STAGE

Reference	*No. of patient*	*Results*
1. Hingson and Edwards[10]	33	No comment
2. Block and Rochberg[4]	39	Estimated blood loss less
3. Block and Rotstein[5]	61	"Less than average bleeding"
4. Siever and Mousel[35]	300	"Considerably less blood is lost"
5. Lyons and Hansen[25]	200	No comment
6. McCormick[27]	100	"Less than with other methods"
7. Lull[23]	500	"Average in the last 500 cases was 111 cc."
8. McElroy and Donnelly[28]	162	196 cc.
9. Jarvis[19]	56	Measured average (29), 245 cc.; estimated (17), 208 cc.; estimated (10), 225 cc.

The uterine motility of the third stage of labor is said to be unusually satisfactory under caudal analgesia, and as a consequence, the blood loss

is small. On the other hand, the frequency of incarceration of the placenta is increased. Vaux and Mitchell[38] and Lull[23] have reported a very small blood loss during the third stage under continuous caudal analgesia. An evaluation of the blood loss in the third stage should not be made without due account being taken of the conditions under which the blood loss was measured. We have observed a greater loss than Vaux and Mitchell, and have attributed our higher average loss to the fact that the majority of deliveries were conducted by internes and externes. Almost all observers are agreed, however, that the blood loss is small under caudal analgesia and that the third stage is short and satisfactory in most cases.

DURATION OF LABOR

Reference	*No. of patients*	*Results*
1. Hingson and Edwards[10]	33	"Cervix seemed to dilate more rapidly"
2. Block and Rochberg[4]	39	Average total labor in primipara, 3 hours; average total labor in multipara, 2 hours
3. Block and Rotstein[5]	61	Average time from injection to delivery in primipara, 4 hours; in multipara, 2 hours
4. Siever and Mousel[35]	300	"Over-all length of labor is increased" Precaudal average, 8 hour; caudal average, 14 hours
5. Lyons and Hansen[25]	200	No comment
6. McCormick[27]	100	Labor shortened
7. Lull[23]	553	Average first stage in primipara, 8 hours
8. McElroy and Donnelly[28]	162	*1st* *2nd* *3rd* Primipara 6:10 1:42 :06 Multipara 4:37 :43 :04
9. Jarvis[19]	70	Primipara—average dilatation when injected 5.3 cm.; delivery 1:54 hours after injection Average first stage 11:18, second stage 1:03, third stage :09 Multipara—average amount of dilatation on injection 4.6 cm.; average time to delivery 1:54 hours Average first stage 9:45, second stage :27, third stage :10

The wide variation in the duration of labor quoted above can be explained on the basis of different definitions of the length of labor. A shortened labor has been attributed to almost every new analgesic agent. Improved uterine motility and relaxation of the cervix would, perhaps, decrease the duration of labor. Unfortunately no objective evidence has been advanced to show that any analgesic agent has such an effect on the cervix. Uterine motility, on the other hand, has been registered objectively. Tocographic studies have shown that no essential change takes place in the rate or character of uterine contractions during serial caudal analgesia.[12,30]

Summary. Continuous or serial caudal analgesia is one of the most important advances in obstetrical analgesia since Simpson introduced the use of ether in 1847. The advantages of caudal analgesia during labor are so desirable that every effort should be made to eliminate any hazards inherent in the method.

It provides complete and dramatic pain relief in a large percentage of the patients when administered by experts. It relaxes the pelvic floor to a marked degree which is especially beneficial in cases of premature labor and when forceps are required. It is less depressing to fetal respiration than many of the other pain-relieving drugs. All of these features are highly desirable.

On the other hand, its use is attended by certain dangers. The first and foremost is the maternal risk. This has been emphasized by McCormick,[27] Block and Rochberg[4] and Studdiford commenting on Lull's[23] report. The administration of any depressant drug into the spinal canal carries with it a certain amount of risk. The chief maternal dangers of caudal analgesia are: (*a*) unrecognized subarachnoid tap, (*b*) the administration of massive doses of anesthetic drug, (*c*) infection in and about the spinal cord, (*d*) unexplained peripheral vascular collapse and, finally (*e*) sensitivity to the anesthetic solution.

Another disadvantage of caudal analgesia is the increased risk to the fetus. Although it is accompanied by less fetal respiratory depression, the rate of operative delivery is increased markedly. Simple operative procedures are easily carried out under caudal analgesia because of the marked pelvic floor relaxation which it provides. On the other hand, the increase in the number of posterior occiput positions, the number of infants in which the presenting part becomes arrested in the transverse position implies an increase in the number of more serious forceps applications.

The increased risk to the fetus and to the mother are important arguments against the use of caudal analgesia. However, they do not necessarily preclude a further study of this method with the hope that these dangers may be eliminated.

The obvious conclusion of these observations is that in spite of recent innovations in the field of obstetrical analgesia, the ideal is yet to be found.

REFERENCES

(1.) **Adams, R. C., Lundy, J. S.,** and **Sheldon, T. H.**: J. Am. Med. Assn., **122**, 152, 1943. (2.) **Batten, D. H.**: Anesth. and Analg., **22**, 143, 1943. (3.) **Barlow, O. W., Climenko, D. R.,** and **Homburger, E.**: Proc. Soc. Exp. Biol. and Med., **49**, 11, 1942. (4.) **Block, N.,** and **Rochberg, S.**: Am. J. Obst. and Gynec., **45**, 645, 1943. (5.) **Block, N.,** and **Rotstein, M.**: J. Am. Med. Assn., **122**, 582, 1943. (6.) **Calvo, J. D.**: Arch. Clin. Obst. y Gynec. ("Eliseo Canton"), **1**, 291, 1942. (7.) **Cleland, J. G. P.**: Surg., Gynec. and Obst., **57**, 51, 1933. (8.) **Cosgrove, S. A.**: Am. J. Obst. and Gynec., **14**, 751, 1927. (9.) **Duquid, A. M. E.,** and **Heathcote, R. St. A.**: Quart. J. Pharm. and Pharmacol., **13**, 318, 1940. (10.) **Edwards, W. B.,** and **Hingson, R. A.**: Am. J. Surg., **57**, 459, 1942. (11.) **Fitzgerald, J. E.,** and **Webster, A.**: J. Am. Med. Assn., **119**, 1082, 1942. (12.) **Frankel, D. S.**: Personal communication. (13.) **Gallen, B.,** and **Prescott, F.**: Brit. Med. J., **1**, 176, 1944. (14.) **Gilbert, G.,** and **Dixon, A. B.**: Am. J. Obst. and Gynec., **45**, 320, 1943. (15.) **Gruber, C. M., Hart, E. R., Gruber, C. M., Jr.**: J. Pharm. and Exp. Ther., **73**, 319, 1941. (16.) **Hartman, M. J.**: Pennsylvania Med. J., **45**, 236, 1941. (17.) **Hingson, R. A.,** and **Edwards, W. B.**: J. Am. Med. Assn., **123**, 538, 1943. (18.) **Irving, F. C., Berman, S.,** and **Nelson, H. B.**: Surg., Gynec. and Obst., **58**, 1, 1934. (19.) **Jarvis, S. M.**: Am. J. Obst. and Gynec., **47**, 335, 1944.

(20.) **Karp, M.,** and **Richardson, G. C.**: Surg. Clin. North America, **23**, 59, 1943. (21.) **Kirschbaum, H. M.**: Am. J. Obst. and Gynec., **44**, 664, 1942. (22.) **Kroger, W. S.,** and **DeLee, S. T.**: Am. J. Obst. and Gynec., **46**, 655, 1943. (23.) **Lull, C. B.**: Am. J. Obst. and Gynec., **47**, 312, 1944. (24.) **Lund, C. J.,** and **Harris, J. W.**: Am. J. Obst. and Gynec., **45**, 980, 1943. (25.) **Lyons, H.,** and **Hansen, F. M.**: Am. J. Obst. and Gynec., **47**, 105, 1944. (26.) **Manalan, S. A.**: J. Indiana Med. Assn., **35**, 564, 1942. (27.) **McCormick, C. O.,** *et al.*: Am. J. Obst. and Gynec., **47**, 297, 1944. (28.) **McElroy, R. C.,** and **Donnelly, J. F.**: Personal communications. (29.) **Mengert, W. F.**: Am. J. Obst. and Gynec., **44**, 888, 1942. (30.) **Murphy, D. P.**: Personal communication. (31.) **Ploss, H. H., Bartels, M.** and **Bartels, W. P.**: Woman, St. Louis, C. V. Mosby, 1937. (32.) **Ruch, W. A.**: Am. J. Obst. and Gynec., **35**, 830, 1938. (33.) **Schumann, W. R.**: Am. J. Obst. and Gynec., **47**, 93, 1944. (34.) **Shumacker, H. B., Manahan, C. P.,** and **Hellman, L. M.**: Am. J. Obst. and Gynec., **45**, 129, 1943. (35.) **Siever, J. M.,** and **Mousel, L. H.**: J. Am. Med. Assn., **122**, 424, 1943. (36.) **Stander, H. J.**: Williams' Obstetrics, New York, D. Appleton-Century, 1941. (37.) **Thomas, H.,** and **Taylor, H. C.**: Connecticut Med. J., **6**, 322, 1942. (38.) **Vaux, W. N.,** and **Mitchell, R. M.**: J. Am. Med. Assn., **124**, 549, 1944. (39.) **Weintraub, F.,** and **Merriam, M. S.**: Am. J. Obst. and Gynec., **46**, 836, 1943. (40.) **Woodbury**: Quoted by Gallen, B., and Prescott, F.: See Ref. 13.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF APRIL 18, 1944

Prevention of Absorption and of Convulsions by Mercurial Diuretics. R. BEUTNER, B. CALESNICK and P. BRADLOW (Dept. of Pharmacology, Hahnemann Medical Coll.). The convulsions from procaine, picrotoxin or strychnine are inhibited when salyrgan or mercurin are added to the solution of the convulsant prior to injection but not on separate injection. Addition of theophylline to the salyrgan or mercurin abolishes this inhibition. The absorption of a diffusible dye like phenol red from the muscle into the blood stream is delayed when mercurin or salyrgan is added to the solution of that dye, but not on separate injection. If theophylline is also added there is no such delay of absorption. After intravenous injections, in rabbit, or after lymph sac injection, in frogs, the 3 convulsant drugs named will lead to convulsions even if salyrgan or mercurin is directly added. Diffusion experiments through parchment or rabbit's bladder show that there is no formation of a non-diffusible compound in this case since salyrgan or mercurin has no influence on the *in vitro* diffusion. The diffusion of phenol red through parchment is insignificantly accelerated by salyrgan and left unchanged by mercurin. Histologic studies indicate that salyrgan may have a protein coagulating effect *in vivo*. The antagonistic effect of theophylline, described above, seems to be due to a prevention of protein coagulation by the theophylline, as can be demonstrated in simple precipitation tests on serum proteins.

In conclusion: Mercurial diuretics inhibit absorption at the site of injection. Naturally they also inhibit their own absorption—the mercurial diuretic stays at the site of injection producing inflammation, so that some of it fails to reach the kidney. This can be avoided by addition of theophylline as is now invariably done in medical practice. It is unlikely that the described local effect of these mercurials is of importance for their diuretic effect.

Ketone Body Formation From Fatty Acids, Using Heavy Carbon as a Tracer. SIDNEY WEINHOUSE, GRACE MEDES and NORMAN FLOYD (The Lankenau Hospital Research Institute, Philadelphia). n-Octanoic acid containing 5.5% of the heavy carbon isotope, C^{13} in the carboxyl group, was incubated with liver slices from fasted rats. The resultant acetoacetic acid was broken down to acetone and CO_2, and the C^{13} content of each fraction determined. The excess C^{13} was found to be distributed equally between the acetone and carboxyl moieties. According to the classical theory of β-oxidation the ketone bodies arise from the terminal 4-carbons and hence should contain no excess isotope. According to the theory of multiple alternate oxidation, oxidation occurs at alternate carbons throughout the fatty acid chain prior to splitting into 4-carbon units; thus the resultant acetoacetic acid should contain the excess isotope exclusively in the carboxyl group.

The observed distribution of the carbon isotope in the acetoacetic acid provides unequivocal evidence for a mechanism of ketone body synthesis

involving β-oxidation throughout the fatty acid chain, followed by a random coupling of the 2-carbon units. A similar experiment with carboxyl-labeled butyric acid indicates that the same mechanism is followed in the formation of acetoacetic acid from this fatty acid.

Only a small portion of the isotopic octanoic acid which disappeared could be accounted for by the formation of ketone bodies or by complete oxidation to CO_2. The results of the experiments indicate that most of the octanoic acid utilized must have undergone a non-oxidative reaction leading to its fixation in the tissue.

The Oxygen Metabolism of the Monkey's Brain in Vivo. CARL F. SCHMIDT, HARRY H. PENNES and SEYMOUR S. KETY (Department of Pharmacology, Univ. of Penna.).* In rhesus monkeys, lightly anesthetized with nembutal supplemented by pentothal as required, cerebral blood flow was measured by a method previously described (*Am. J. Physiol.*, **138**, 421, 1943) during the collection of samples of arterial and cerebral venous (jugular bulb) blood, which were analyzed for O_2, CO_2 and glucose content. The most important results were as follows:

1. *The magnitude of cerebral oxygen consumption under "normal" conditions.* In the 9 animals showing greatest signs of cerebral activity (corneal reflex active, spontaneous movements, vigorous respiration, good blood pressure) this averaged 3.6 ± s.d. 0.7 cc. O_2 per 100 gm. of brain (wet weight) per minute, corresponding with a QO_2 of 10.8; the cerebral arteriovenous oxygen differences averaged 8.1 ± s.d. 1.4 vols. %. The cerebral blood flows averaged 45.6 ± s.d. 12.4 cc. per 100 gm. per minute. The blood pressures varied from 84 to 135 and averaged 118 mm. Hg. The cerebral respiratory quotients averaged 0.97. The oxygen consumed by the brain averaged 9.5 ± s.d. 1.8% of the animal's total oxygen consumption.

2. *Variations in cerebral oxygen consumption under different circumstances.* The various observations can be grouped, according to the existing state of cerebral activity, as follows:

Group 1, in which respiration had ceased, vasomotor depression was present, and all reflexes had disappeared. Cerebral oxygen consumption in this group averaged 1.66 ± s.d. 0.8 cc. per 100 gm. per minute.

Group 2, in which breathing was present though abnormally slow but no reflexes could be detected. Here cerebral O_2 uptake averaged 2.56 ± s.d. 0.79 cc. per 100 gm. per minute.

Group 3, with active circulation, respiration and reflexes. Cerebral oxygen consumption in this group averaged 3.79 ± s.d. 0.94 cc. per 100 gm. per minute. The differences among these 3 mean values are statistically significant.

Stimulant drugs (metrazol, picrotoxin) increased cerebral O_2 consumption consistently when convulsions occurred, but had no effect otherwise. Pentothal decreased cerebral O_2 consumption while depressing respiration and reflex activity.

Intentional decrease in cerebral blood flow by bleeding was associated with an increase in the cerebral arteriovenous oxygen difference. As long as the latter could nearly compensate for the former and prevent a considerable fall in the cerebral oxygen uptake, functional activity was retained, but once cerebral O_2 uptake began to fall, reflexes were quickly lost and respiration became slower or ceased entirely. When the blood was rein-

* Work done under contract with the Office of Scientific Research and Development.

jected, some animals showed complete recovery and some did not; in the former, cerebral O_2 consumption came back to or above the control level, while in the latter it did not. These findings confirm those previously made in dogs (*Am. J. Physiol.*, **84**, 223, 1928).

3. *Correlations among cerebral metabolism, cerebral blood flow and cerebral A-V oxygen difference.* As between the A-V oxygen difference and cerebral blood flow (corrected for difference in blood pressure), there is no trace of significant correlation ($r = 0.02$). Between A-V oxygen difference and cerebral metabolism a fairly significant correlation exists ($r = 0.44$). The best correlation is between the cerebral metabolism and cerebral blood flow ($r = 0.636$). This strongly suggests that there is an intrinsic mechanism whereby the tone of the cerebral blood-vessels is adjusted to the metabolic requirements of the brain. If so, cerebral A-V oxygen differences cannot be interpreted in terms of cerebral blood flow, for if this mechanism functions properly changes in the A-V oxygen difference will be prevented by vascular readjustments and any changes that occur will signify only that the adjustments were not completely adequate. Changes in the A-V difference tended to parallel cerebral metabolic changes, but not uniformly; the A-V oxygen difference was increased in some experiments by both metrazol (or picrotoxin) and pentothal although cerebral metabolism was increased by the former and decreased by the latter.

4. *Relation of these to other figures for cerebral metabolism.* The QO_2 in our best experiments ranged from 7.5 to 13.5 and averaged 10.8. These figures are much smaller than any previously reported for the metabolism of the brain *in vivo* (*Am. J. Physiol.*, **140**, 190, 1943), the QO_2 values ranging from about 17 to 39. Since ours are the only experiments in which reasonably accurate blood flow measurements have been made we attribute the higher figures reported by others to overvaluation of the blood flow factor, because of escape of blood to extracranial areas or other technical defects. Figures for the QO_2 of cortical slices or homogenates *in vitro* range from 10.7 to 15.5, which is about the order of our highest values. At present we do not know whether this agreement is fortuitous or significant because we do not know how much of the metabolism and blood flow measured in our experiments represents cortical activity, or how much the anesthetic might be expected to depress the QO_2 in our experiments.

Observations on the Anticephalin Activity of Normal and Hemophilic Plasmas. L. M. Tocantins (Division of Hematology, Jefferson Medical Coll., Philadelphia). Exposure of plasma to adsorbents (asbestos fibers, kaolin, infusorial earth, pumice stone) reduces its anticephalin activity. Contact of 1 cc. of plasma for 60 minutes at 20° C. with 50 mg. or more of asbestos fibers removes most of the prothrombin and some of the fibrinogen from the plasma. By adjusting the conditions of the contact exposure, it is possible to remove most of the anticephalin, without greatly disturbing the other clotting factors. Such "adsorbed plasmas," whether normal or hemophilic, behave alike towards cephalin, clot spontaneously, though slowly, even in the presence of citrate, and at approximately the same rate whether in glass or paraffin coated tubes. The rate of conversion of hemophilic prothrombin into thrombin by cephalin is slower than normal. Dilution of the plasma (1–20, 1–30) equalizes the rate of conversion and nearly effaces the difference in behavior towards cephalin between normal

and hemophilic plasmas. The prothrombin conversion rate of "adsorbed plasma" is faster than normal. Higher dilutions (1–60, 1–80) are necessary to equalize the prothrombin conversion rate of normal plasma with that of "adsorbed plasma." Prothrombin estimations done on "adsorbed plasma" by the 1-stage method (Quick) yield higher values than by the 2-stage method (Smith). The increase in the prothrombin conversion rate which seems to follow removal of anticephalin from the plasma may explain this disagreement between the results obtained by the 2 methods.

Depressor Effect of Cold Upon the Static Receptors of the Labyrinth. E. A. SPIEGEL (Dept. of Exp. Neurology, Temple Univ. School of Medicine, Philadelphia). A u-shaped cannula introduced into the external and middle ear of decerebrate cats was perfused with water of from 3° to 20° C. Water of 9° or below produced within a few minutes a decrease in the muscle tone of the homolateral foreleg, causing a drooping of this leg. This effect may outlast the calorization, but is reversible. Similar, although less pronounced, effects were observed in rabbits with intact brain. The effect of unilateral cooling upon the posture of the head was demonstrated in unanesthetized rabbits and in cats under bulbocapnine catalepsy. The cold temporarily produced effects similar to those of unilateral labyrinth paralysis: a rotation of the head about the oro-occipital axis, the affected ear lying lower. The excitability of the cristæ revealed no significant difference of the postrotatory nystagmus in cats rotated before and during prolonged application of cold to both ears. Thus a depressor effect of cold could be observed only on static receptors influencing the posture of head and extremities (apparently chiefly the maculæ), while such an effect upon the receptors reacting to angular acceleration was not noticeable. The possible rôle of physical factors is discussed (change in specific gravity of the endolymph altering the otolithic pressure upon the macula).

BOOK REVIEWS AND NOTICES

CLINICAL DIAGNOSIS BY LABORATORY EXAMINATIONS. By JOHN A. KOLMER, M.S., M.D., DR.P.H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine in the School of Medicine and the School of Dentistry of Temple Univ.; Director of the Research Institute of Cutaneous Medicine; Formerly Professor of Pathology and Bacteriology in the Graduate School of Medicine of the Univ. of Penn. Pp. 1239; 75 figs. New York, London: D. Appleton-Century, 1943. Price, $8.00.

THIS new work, by a well-known writer of successful articles and textbooks, is presumably an outgrowth from his earlier books, "Infection, Immunity, and Specific Therapy" and "Approved Laboratory Technique" (with Boerner), with which there is necessarily considerable overlap. In its Part 2, "The Practical Applications of Laboratory Examinations in Clinical Diagnosis," however, it cultivates new ground. Here, the expected laboratory findings are given for a number of important diseases. For instance, in the chapter on Diseases of the Blood and Hemopoietic System (57 pages), some 40 odd diseases are considered. The high points of each are presented in one or more opening paragraphs, then the laboratory tests to be used and the results to be expected. This will undoubtedly be a useful and convenient form of presentation for many clinicians who do not feel up to date in their knowledge of the application of laboratory tests to clinical medicine. It should hardly be necessary to point out that the picture of the disease itself is of course far from adequate, nor is it meant to be. Yet the slothful might be tempted to make it substitute for the more complete treatment given in the conventional textbooks of medicine.

Part I, the larger half of the book, covers "the clinical interpretation of laboratory exams." Here, brief statements about the normal condition of the material in question are followed by descriptions of the various changes observed—often in convenient tabular form—how they are brought about, and their significance. There is also a shorter section on the technique of laboratory exams. Thus, the book contains material of value to clinicians, laboratory diagnosticians and technicians, and teachers and students of "clinical pathology."

One is chiefly struck by the amount of information offered—the Table of Contents covers 32 pages, for example, and the Index 130 pages. One wonders that a single individual—and a busy one at that—could have collected such a mass of information covering so many fields; and one should not be surprised that the book has more than the average number of typographic errors and statements which many will find incorrect or open to question. Relatively, these are few, however, and more than outweighed by the book's good points.

E. K.

THE HIPPOCRATIC OATH. Text, Translation and Interpretation by LUDWIG EDELSTEIN. Supplements to the Bull. of Hist. of Med., Editor: HENRY E. SIGERIST, No. 1. Pp. 64. Baltimore: Johns Hopkins Press. Price, $1.25.

THIS is the first of a series of Monographs, published occasionally as supplements to the *Bulletin of the History of Medicine*. The series which has been in prospect for some years aims to accommodate articles too long for the *Bulletin*, but not long enough to be published as independent monographs. The supplements are sold independently and at reduced prices to those already receiving the *Bulletin*. We congratulate the Institute on the achievement of this new series.

Dr. Edelstein, a recognized authority on Greek medicine, presents a detailed and well-documented interpretation of the famous Oath, an interpretation derived chiefly from the regulations about poisons and abortions. It is regarded as a Pythagorean document, composed not before or after the 4th century, *i. e.*, like so much of the Corpus Hippocraticum, not the work of the great Hippocrates himself. The Author states positively that the Oath was not at first accepted by all, but that it began to be popular at the end of antiquity, eventually to become "the nucleus of all medical ethics."

E. K.

THE RELIGIOUS AND PHILOSOPHICAL ASPECTS OF VAN HELMONT'S SCIENCE AND MEDICINE. By WALTER PAGEL. Supplements to the *Bull. of Hist. of Med.*, No. 2, Editor: HENRY E. SIGERIST. Pp. 44. Baltimore: Johns Hopkins Press. Price, $1.00.

VAN HELMONT'S contributions to medical progress as an iatrochemist and explainer of vital phenomena in chemical terms and his invention of the word and concept "gas" are well known. His contributions to philosophy, however, are, in the opinion of the Author, poorly comprehended and appreciated. This he aims to rectify, integrating van Helmont's religio-philosophic with his scientific side, in order to present a true picture of the whole of van Helmont's study of life.

E. K.

A SURGEON'S WORLD. An Autobiography. By MAX THOREK, M.D. Pp. 410. Philadelphia, New York: J. B. Lippincott, 1943. Price, $3.75.

"A SURGEON'S WORLD" is the full-length autobiography of the eminent, Hungarian-born, American surgeon, Max Thorek. It is an intimate account of his life from his earliest remembrances as a boy in his native town among the Tatra Mountains, as a student in Budapest, and as an immigrant and citizen in the land of great opportunity—America! The story is excellently written, and as he relates the experiences and problems that confronted him during his life as a member of the medical profession, one cannot help but "live" along with the Author.

Throughout the entire story, the reader appreciates and observes the philosophy of Dr. Thorek's life which is unique among those who were born and reared on "the battleground of Europe" and who subsequently came to America where freedom and opportunity are the heritage of everyone.

The book is filled with many interesting anecdotes of both a professional and a humanitarian nature that are constantly confronting a surgeon. At the end of the book, Dr. Thorek gives a short résumé of the outstanding pioneers in the field of medical science from the time of Hammurabi to the present. This list is conspicuous, however, by the absence of the immortal names of Marie and Pierre Curie, and one questions the wisdom of trying to cover such a big topic in this way and in a book of this kind.

This book is a doctor's book which tells of Dr. Thorek's work, those who helped him as well as those who were helped by him. It is forthright, impartial and unaffected. It reflects a fine gusto for life and activity and a point of view that is as aware of the humorous as of the pitiable. It is an entertaining book and the many people who are destined to read it shall consider the time profitably spent.

H. S.

WHAT IS HYPNOSIS: Studies in Auto and Hetero Conditioning. By ANDREW SALTER. Pp. 88. New York: Richard R. Smith, 1944. Price, $2.00.

"HYPNOSIS is the production of reactions in the human organism through the use of verbal or other associative reflexes." Continuing, the writer proceeds to show that it is but a conditioned reflex. Thus is "suggestion" thrown to the discard and Pavlov's "conditioned response" assigned to its place. The chapters are: What is hypnosis? a further consideration of

hypnosis; preliminary experiments in autohypnosis; a study of Group III; appendix: three techniques of autohypnosis.

"Rapport" is considered an obsolete word; "hypnotist" is an unfortunate term; and a more appropriate designation for "conditioned reflex" it is said would be "associative reflex." Previously, it had been believed that through hypnosis persons could not be impelled to commit crimes; but now, "hypnotized subjects have stolen money, rushed to pick up rattlesnakes, and thrown sulphuric acid into a man's face, which, unknown to the subject was protected by invisible glass." That such a menacing agent may not be released in our midst seems assured, however, since it is said, "I doubt that at present more than half a dozen persons in this country could command technique sufficient to do so."

Finding an appropriate answer to this interrogatory title is admittedly difficult; nevertheless, the Author believes it has been achieved. A weakness of the theme is a tendency to employ chiefly those references that support the Author's views. N. Y.

HUMAN CONSTITUTION IN CLINICAL MEDICINE. By GEORGE DRAPER, M.D., Associate Professor of Clinical Medicine, Coll. of Physicians and Surgeons, Columbia Univ.; Associate Attending Physician, Presbyterian Hospital, New York City; C. W. DUPERTUIS, PH.D., Physical Anthropologist, Constitution Clinic, Presbyterian Hospital, New York City; and J. L. CAUGHEY, JR., M.D., MED.SCI.D., Associate in Medicine, Coll. of Physicians and Surgeons, Columbia Univ.; Assistant Physician, Presbyterian Hospital, New York City. Pp. 273; 28 figs.; 30 tables. New York, London: Paul B. Hoeber, Med. Dept. of Harper & Brothers, 1944. Price, $4.00.

THIS book represents an attempt to define the man within the patient. In the end failure is admitted, since the spirit of man is imponderable. At the same time, on the basis of morphology, physiology, immunity and emotion, a good case is made out for the primary thesis: that disease depends not merely on the nature of the external injurious agent and the usual disease process but equally on the nature of the total personality of the particular person affected. This leads the Authors into a detailed description and discussion of genetics, androgyny (the composite of masculine and feminine characteristics), anthropometry, somatotypes, constitutional physiology and psychology. They wisely point out the importance of a broad cultural background for the practice of medicine and show how the man within the patient, instead of obstructing the healer's efforts, may, if properly understood, become his effective ally. The book should be read by every student of medicine in his effort to develop a good "bedside manner," which the Authors define as "a distillate of objectivity, intuition, common sense and good manners." More important, however, is this successful adaptation to clinical practice of the known facts in the study of the constitution, a necessarily detailed and protracted field of study in which the senior author has been outstanding for many years. R. B.

THE SEXUAL GLANDS OF THE MALE. By OSWALD SWINNEY LOWSLEY, A.B., M.D., F.A.C.S., Collaborators: FRANK HINMAN, A.B., M.D., F.A.C.S., DONALD R. SMITH, A.B., M.D., and ROBERT GUTIERREZ, A.B., M.D., F.A.C.S., Reprinted from Oxford Loose-Leaf Urology. Pp. 619; 4 tables; 59 figs. New York: Oxford Univ. Press. Price, $10.00.

THIS book, written by well-known authors in the urologic field, is composed of material reprinted from the "Oxford Loose-Leaf Urology." Because knowledge concerning the sexual glands of the male has accumulated so rapidly in the past decade, it is of considerable value to have this information in a single volume. Much of the subject matter recorded is from the original works of the Authors. However, there is extensive citation of the literature. Bibliographies follow each section of the book.

Dr. Lowsley writes the section on the prostate gland; Drs. Hinman and Smith, the section on the testicle and epididymus; and Dr. Gutierrez, the section on the seminal tract and spermatic cord. Illustrations are by Mr. William P. Didusch.

In each of the sections the embryology, anatomy, physiology and pathology of the particular organ being discussed are presented. The latest methods of surgical and non-surgical therapy are discussed as each organ is presented. The author's personal methods of treatment are emphasized, but opinions of others recorded in the literature are given on controversial subjects.

The book appears to be written primarily for those interested in a specialized knowledge of the genital tract of the male. It should prove valuable as an authoritative reference to the urologist, general surgeon and endocrinologist.

L. LaT.

AUTHORITY IN MEDICINE: OLD AND NEW. By MAJOR GREENWOOD, D.Sc., F.R.C.P., F.R.S., Professor of Epidemiology and Vital Statistics in the Univ. of London. The Linacre Lecture, May 6, 1943. Pp. 32. Cambridge: Univ. Press; London: Bentley House; New York: Macmillan, 1943. Price, $.40.

WE are gland to commend this essay to our readers. Pertinently for a Linacre Lecture, it considers Galen, the authoritative—with a kind word for his interpreter, Linacre—but it is Galen in the true original, not in the perverted and shrivelled authoritarianism that has been handed us by the Middle Ages. Galen on personal hygiene, dietetics, physical training, and as a medical psychologist usually gave sound practical advice, though his reasons for it often were fallacious. At any rate, he was by no means the dogmatist that we have been led to believe by his commentators of 1000 years.

Major Greenwood, a thorough believer in the experimental method, nevertheless recognizes its limitations and apparently agrees with Raymond Pearl that "of all methodological procedures in biology, the *experimentum crucis* is the most dangerous;" and that many such, loudly hailed, have later proved to have led to false conclusions. Yet, he foresees a future for experimental epidemiology, especially on statistical lines. The essay concludes with a consideration of "the authority of intention," upholding the zealous maintenance of pure research and intellectual freedom.

E. K.

THE RIDDLE OF CANCER. By CHARLES OBERLING, M.D. Translated by WILLIAM H. WOGLOM, M.D. Pp. 196. New Haven: Yale Univ. Press; London: Oxford Univ. Press, 1944. Price, $3.00.

PROFESSOR OBERLING is a distinguished student of cancer, well qualified from personal experience to write upon this subject. In addition, his unusual ability to write and to teach make him peculiarly fitted to present the subject of cancer in a readable and understandable manner. Dr. Woglom has done an excellent job of translating. This little volume traces the development of our concepts of cancer from the earliest available records to the most modern hypotheses, concisely and clearly and with a commendable absence of irrelevant material. Three hypotheses are presented, the irritational, the embryonal and the microbic or parasitic. The bulk of the book is devoted to experimental cancer. Transplantable tumors are considered in some detail; as are also induced tumors. Of the latter, the greatest emphasis is laid upon the carcinogenic viruses; Professor Oberling's main theme throughout the book is an enthusiastic support of the virus hypothesis as the cause of cancers in general. As he states it, "Either we must agree that there are many different kinds of malignant growth, and thus be free to admit as many causes as we wish; or that there is but one malignant process, in which case the virus hypothesis becomes the only logical solution." In answer to those who may be inclined to criticize the author for his whole-hearted acceptance of the virus hypothesis, his closing sentence is addressed: "To those who may be inclined

to reproach the author for a too enthusiastic partisanship he would reply that it is never ill judged to be guided by a hypotheses so long as it does no violence to the known facts, and that the best proof of value is the amount of research stimulated. Submitted to these tests, the virus hypothesis has nothing to fear."

To the Reviewer the greatest value of the book lies in the separation of the grain from the chaff in the data obtained upon cancer by research. The significant material is included and carefully interpreted. The layman may meet with difficulty in understanding some of the terminology and some of the reasoning may also leave him confused upon the first reading; but from it all he should be able to grasp the essentials. For the medical student, physician, and even for the cancer investigator, the book holds a wealth of material in its relatively few pages. The Reviewer enthusiastically recommends it to everyone interested in our present-day concepts of cancer. D. C.

A TEXT-BOOK OF PATHOLOGY. Edited by E. T. BELL, M.D. Contributors: E. T. BELL, M.D., Professor of Pathology, Univ. of Minnesota; B. J. CLAWSON, M.D., Professor of Pathology, Univ. of Minnesota; and M. S. MCCARTNEY, M.D., Associate Professor of Pathology, Univ. of Minnesota. Fifth ed. Pp. 862; 448 figs. (4 color plates). Philadelphia: Lea & Febiger, 1944. Price, $9.50.

THE 5th edition of this text represents a thorough revision and the introduction of much new material, yet with a reduction of 69 pages. Of particular interest is the inclusion of recent work on blast injuries and infectious diseases of interest in war medicine. B. J. Clawson has contributed the chapter on Diseases of the Heart, and J. S. McCartney, the chapters on The Mycoses, and on Diseases of the Liver and Gall Bladder. Even in a single volume text-book of this size, there are omissions of material that, to the Reviewer, should be included. Also, the quality of the illustrations is occasionally unsatisfactory, and one misses a statement of magnifications and stains in the legends. Useful bibliographies are appended at the end of each chapter, though, in not a few instances, they are not sufficiently up to date. This book, however, appeals to the Reviewer as a generally sound and readable text and should fulfill the Authors' desire to furnish medical students with a text-book which may be of use during the clinical years as well as during their course in pathology. D. C.

NEW BOOKS

Anatomy and Physiology. Laboratory Manual. By CATHERINE PARKER ANTHONY, B.A., R.N., Instructor of Anatomy and Physiology, Lutheran Hospital; Formerly Instructor of Anatomy and Physiology, St. Luke's Hospital, and Assistant Instructor of Anatomy and Physiology, Frances Payne Bolton School of Nursing, Western Reserve Univ., Cleveland, Ohio. Pp. 249; many illus. St. Louis: C. V. Mosby, 1944. Price, $2.00.

The Jews and Medicine Essays. By HARRY FRIEDENWALD, M.D., D.H.L. (HON.), D.Sc. (HON.), Professor Emeritus of Ophthalmology, Univ. of Maryland. Preface by HENRY E. SIGERIST. Publications of the Institute of the History of Medicine, The Johns Hopkins Univ. First Series: Monographs. Vols. II and III. Pp. 817; many figs. Baltimore: Johns Hopkins Press, 1944. Price, $3.75 per vol.

Allergy in Practice. By SAMUEL M. FEINBERG, M.D., Associate Professor of Medicine and Chief of Division of Allergy, Northwestern Univ. Medical School; President, American Association for the Study of Allergy, 1942–43. With the Collaboration of OREN C. DURHAM, Chief Botanist, Abbott Laboratories. Pp. 798; 36 figs. Chicago: Year Book Publishers, 1944. Price, $8.00.

The Wounded Get Back. By ALBERT Q. MAISEL. Foreword by Ross T. McINTIRE, Rear Admiral, M.C., U. S. N., The Surgeon-General of the Navy. Pp. 230. New York: Harcourt, Brace, 1944. Price, $2.50.

The Brush Foundation Study of Child Growth and Development. 1. Psychometric Tests. By ELIZABETH EBERT and KATHERINE SIMMONS. Monographs of the Society for Research in Child Development, Vol. VIII, No. 2, Serial No. 35. Pp. 113; 19 figs.; 70 tables. Washington, D. C.: National Research Council, 1943. Price, $1.50.

Small Community Hospitals. By HENRY J. SOUTHMAYD, Director, Division of Rural Hospitals, The Commonwealth Fund; and GEDDES SMITH, Associate, The Commonwealth Fund. Foreword by BARRY C. SMITH, General Director, The Commonwealth Fund. Pp. 182. New York: The Commonwealth Fund, 1944. Price, $2.00.

The War and Mental Health in England. By JAMES M. MACKINTOSH, M.D., Professor of Preventive Medicine, University of Glasgow. Pp. 91. New York: The Commonwealth Fund, 1944. Price, $.85.

Synopsis of Neuropsychiatry. By LOWELL S. SELLING, Sc.M., M.D., PH.D., DR.P.H., Director, Psychopathic Clinic, Recorder's Court, Detroit Mich.; Associate Attending Neuropsychiatrist, Eloise Hospital; Adjunct Attending Neuropsychiatrist, Harper Hospital. Pp. 500; numerous figs. and tables. St. Louis: C. V. Mosby, 1944. Price, $5.00.

Virus Diseases in Man, Animal and Plant. A Survey and Reports Covering the Major Research Work Done During the Last Decade. By GUSTAV SEIFFERT. Translation by MARION LEE TAYLOR, PH.D. Pp. 332; 7 figs.; 7 tables. Published upon recommendation of the National Research Council. New York: Philosophical Library, 1944. Price, $5.00.

NEW EDITIONS

Clinical Urology. By OSWALD SWINNEY LOWSLEY, A.B., M.D., F.A.C.S., Director of Dept. of Urology (James Buchanan Brady Foundation) of the New York Hospital; and THOMAS KIRWIN, M.A., M.S., M.D., F.A.C.S., Attending Surgeon of Dept. of Urology (James Buchanan Brady Foundation) of the New York Hospital. Drawings by WILLIAM P. DIDUSEH. Second ed. Vols. 1 and 2. Pp. 1884; 220 figs. Baltimore: Williams & Wilkins, 1944. Price, $10 set of 2 Vols.

Textbook of Gynecology. By EMIL NOVAK, M.D., F.A.C.S., Associate in Gynecology, The Johns Hopkins Medical School; Gynecologist, Bon Secours and St. Agnes Hospitals, Baltimore. Second ed. Pp. 708; 456 figs. Baltimore: Williams & Wilkins, 1944. Price, $8.00.

Manual of Urology. By R. M. LECOMTE, M.D., I.A.C.S., Professor of Urology, Georgetown Univ. Medical Department; Member of the American Urological Association. Third ed. Pp. 305; 60 figs. Baltimore: Williams & Wilkins, 1944. Price, $4.00.

The Art and Science of Nutrition. A Textbook on the Theory and Application of Nutrition. By ESTELLE H. HAWLEY, PH.D., and GRACE CARDEN, B.S., The Univ. of Rochester, School of Medicine and Dentistry, Strong Memorial and Rochester Municipal Hospitals, Rochester, N. Y. Second ed. Pp. 668; 139 illus (11 colored); 138 figs.; 68 tables. St. Louis: C. V. Mosby, 1944. Price, $3.75.

The Principles and Practice of Medicine. Originally written by SIR WILLIAM OSLER, BARTO, M.D., F.R.C.P., F.R.S. Designed for the use of practitioners and students of medicine by HENRY A. CHRISTIAN, A.M., M.D., LL.D. (HON.), Sc.D., HON. F.R.C.P. (CAN.), F.A.C.P. Fifteenth ed. Pp. 1498. New York: D. Appleton-Century, 1944. Price, $9.50.

Elimination Diets and the Patient's Allergies. A Handbook of Allergy. By ALBERT H. ROWE, M.D., Lecturer in Medicine, Univ. of California Medical School, San Francisco, Calif.; Consultant in Allergic Diseases, Alameda County Hospital, Oakland, Calif. Second ed. Pp. 256. Philadelphia: Lea & Febiger, 1944. Price, $3.50.

Tropical Nursing. A Handbook for Nurses and Others Going Abroad. By A. L. GREGG, M.A., M.D., M.CH., B.A.O. (DUBLIN), D.T.M. and H. (LOND.), L.M. (ROTUNDA HOSPITAL); Member of Associate Staff of, and Lecturer to Nurses at the Hospital for Tropical Diseases, London; Lecturer on Tropical Diseases, Westminster Hospital Medical School. Second ed. Pp. 185; 13 figs. New York: Philosophical Library, 1944. Price, $3.00.

Synopsis of Diseases of the Heart and Arteries. By GEORGE R. HERRMANN, M.S., M.D., PH.D., F.A.C.P., Professor of Medicine, University of Texas; Director of the Cardiovascular Service, John Sealy Hospital; Consultant in Vascular Diseases, U. S. Marine Hospital. Third ed. Pp. 516; 103 figs.; numerous tables; 103 illus. (4 color plates). St. Louis: C. V. Mosby, 1944. Price, $5.00.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

NEW NOTICE TO CONTRIBUTORS AND SUBSCRIBERS

Activated by a directive from the War Production Board, we have changed the size of our type page for the "duration" to effect an economy in the amount of paper used. While there is a smaller number of pages, the amount of material has not been noticeably reduced.

We hope that any unpleasant effect produced by cutting down the margins will be accepted and approved by readers as a temporary war casualty. It is possible that more radical changes will have to be made later, but we are loath to change any more than absolutely necessary, a format that has existed practically unchanged since the Journal began in 1820.

For the balance of the war, 150 reprints will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150. This modification is for the same reason as the change of format, *i. e.*, conservation of paper.

NOTICE TO SUBSCRIBERS AND ADVERTISERS

We desire to secure several copies of the March and May 1943 numbers of this Journal, in order to comply with requests and need for replacements in long library "runs." The war situation has made it impossible to print extra numbers to supply this demand. We would be *very* grateful to anyone who would return to the Publishers any unmutilated copies of these numbers for which they have no further use, and we would be glad to repay postage.

INDEX

A

Addison's disease with pellets of desoxycorticosterone acetate, Treatment of, 19
Adrenal adenoma with relief of Cushing syndrome, Surgical removal of, 196
Aerosol inhalation, A supplemental note, A study of sulfonamide, 488
Agranulocytosis with complications. Case report, Allergic, 453
Air-borne infection, An apparatus for study of the physiology of, 131
Allergic agranulocytosis with complications. Case report, 453
Allergy. II. The presence in allergic disease of atypical lymphocytes and symptoms suggesting the recovery phase of infectious mononucleosis, Blood studies in, 638
Amebiasis: Analytical study of the cases admitted to a Philadelphia hospital during the last 5 decades, 754
Analgesia in obstetrics, 804
Aneurysm. Rupture into the jejunum preceded by occult blood in the stool, Abdominal aortic, 600
Angina pectoris, Clinical aspects of pain in the chest, 1., 561
Anticephalin activity of normal and hemophilic plasmas, Observations on the, 814
Aortic aneurysm. Rupture into the jejunum preceded by occult blood in the stool, Abdominal, 600
Applebaum, E., Nelson, J., Sulfadiazine and its sodium compound in treatment of meningococcic meningitis and meningococcemia, 492
Athletes as affected by intercollegiate sports, The blood picture of, 130
Auerbach, O., Stemmerman, M. G., The development of pulmonary tuberculosis in congenital heart disease, 219
Avidin (egg white), One year observations of the treatment of cancer with, 733

B

B vitamins in the human subject, Studies of the. VII. Blood pyruvate and lactate-pyruvate ratio following the ingestion of glucose in experimental deficiency, 247
Bacterial control in large spaces, The use of glycol vapors for, 361
Barnebee, J., *see* Koletsky, S., 421
Barnes, Mildred W., *see* Peterson, Osler L., 166
Barnes, T., Electrical potential of human skin measured on the fingers, 550
Base by ion adsorption, Determination of serum total, 129
Bauman, L., Whipple, A., with the technical assistance of Bratti, E., Stines P., The diagnostic value of pancreatic function tests in forty-seven surgically treated cases, 281
Beerman, H., *see* Stokes, J., 540
Beeson, P., Miller, E., Relationship of lymphogranuloma venereum infection to the incidence of hyperglobulinemia, 643
Beutner, R., Calesnick, B., and Bradlow, P., Prevention of absorption and of convulsions by mercurial diuretics, 812
Bigg, E., Jennings, B., Fried, S., Inflammability characteristics of propylene glycol and triethylene glycol in liquid and vapor form, 370
Bigg, E., Jennings, B., Fried, S., The use of glycol vapors for bacterial control in large spaces, 361
Bjorndahl, Oscar, *see* Haydak, M., 209
Blood picture of athletes as affected by intercollegiate sports, The, 130
Blood pressure, The naturally occurring blood sulfocyanates and their relation to, 63
Blue, J., Allergic agranulocytosis with complications. Case report, 453
Boehrer, John J., *see* Haydak, Mykola, 209
Bohning, A., *see* Cole, S., 317
Bradlow, P., *see* Beutner, R., 812
Bratti, E., *see* Bauman, L., 281
Brown, R., *see* Master, A., 435
Burch, G. E., *see* Winsor, Travis, 152

C

Cadaver blood, A note recommending the use of dried plasma obtained from fresh, 314
Calesnick, B., *see* Beutner, R., 812
Cancer with avidin (egg white), One year observations of the treatment of, 733
Carcinoma of the nasopharynx, 342
Cardiac function and coronary insufficiency, The electrocardiogram and the "two-step" exercise. A test of, 435
"Cardiac" or congestive cirrhosis. Pathologic and clinical aspects, 421
Cardiovascular syphilis, Electrocardiographic patterns in, 317
Cardiovascular variables in healthy men, and the relation of physique to these and other variables, Intercorrelations between, 684

Ceccolini, Edward M., *see* Wilburne, Morris, 204
Cell volume, The use of fibrinogen in a rapid method of determining, 29
Cerebral cortex of the monkey, Topical projection of the cochlea to the, 685
Chapple, C., Lynch, H., A study of sulfonamide aerosol inhalation. A supplemental note, 488
Charny, C., The use of equine gonadotropin in male infertility. An analysis of 127 patients, 519
Chlorophyll: An experimental study of its water-soluble derivatives. I. Remarks upon the history, chemistry, toxicity and antibacterial properties of water-soluble chlorophyll derivatives as therapeutic agents, 647
Cholecystographic medium, A new, 678
Chornock, F., *see* Neefe, J., 626
Choroid and retina, Senile changes in the, 258
Churg, Jacob, Wachstein, Max, Osteosclerosis, myelofibrosis and leukemia, 141
Cirrhosis. Pathologic and clinical aspects, "Cardiac" or congestive, 421
Citrated blood in man. III. The effect on temperature and the white blood cell count, Observations on the oral administration of, 465
Clark, J. K., *see* Murphy, F. D., 77
Clinical aspects of pain in the chest. 1. Angina pectoris, 561
Cochlea to the cerebral cortex of the monkey, Topical projection of the, 685
Cold upon the static receptors of the labyrinth, Depressor effect of, 815
Cole, S., Bohning, A., Electrocardiographic patterns in cardiovascular syphilis, 317
Colvin, S., Gore, I., Peters, M., A case of histoplasmosis (Darling) with autopsy, 378
Congenital heart disease, The development of pulmonary tuberculosis in, 219
Convulsions by mercurial diuretics, Prevention of absorption and of, 812
Coronary insufficiency, The electrocardiogram and the "two-step" exercise. A test of cardiac function and, 435
Cushing syndrome, Surgical removal of adrenal adenoma with relief of, 196

D

D'Agati, V., *see* Marangoni, B., 385
D'Agati, V. C., *see* Marangoni, B. A., 67
Derbes, V., *see* Engelhardt, H., 776
Desoxycorticosterone acetate, Treatment of Addison's disease with pellets of, 19
Diabetes, Alloxan, 550
4,4′-diaminodiphenylsulfone, The effects on experimental tuberculosis of, 290
Diastase values in mumps and mumps pancreatitis, Blood, 461
Diaz-Rivera, R., Rasberry, E., Amebiasis: Analytical study of the cases admitted to a Philadelphia hospital during the last 5 decades, 754
Diet for adult humans, A clinical and biochemical study of cow's milk and honey as an essentially exclusive, 209
Digestive tract: A review, Major motility patterns of the child's, 782
Diuretics, Prevention of absorption and of convulsions by mercurial, 812
Donnelly, J., Analgesia in obstetrics, 804
Dowling, H., Lepper, M., "Drug Fever" accompanying second courses of sulfathiazole, sulfadiazine and sulfapyridine, 349
"Drug Fever" accompanying second courses of sulfathiazole, sulfadiazine, and sulfapyridine, 349
Dworzan, H., *see* Rawls, W., 528

E

Electrocardiographic patterns in cardiovascular syphilis, 317
Electroencephalographic studies during fever induced by typhoid vaccine and malaria in patients with neurosyphilis, 512
Elsom, K. O., *see* Klein, D., 247
Engelhardt, H., Derbes, V., Tumefaction of subcutaneous fat following the injection of insulin, 776
"Eosinophilic or solitary granuloma of bone," Hand-Schüller-Christian's syndrome and, 161
Erf, L., A note recommending the use of dried plasma obtained from fresh cadaver blood, 314
Erythrocytes. A specific test for the recognition of Marchiafava's anemia, The "heat resistance" of, 624

F

Fabricant, N., Vasomotor rhinitis, 534
Farris, E. J., The blood picture of athletes as affected by intercollegiate sports, 130
Fat tumefaction of subcutaneous, following the injection of insulin, 776
Feil, H., *see* Thomson, H., 588
Feldman, W., Hinshaw, H., Moses, H., The effects on experimental tuberculosis of 4,4′-diaminodiphenylsulfone, 290
Feldt, R., Sulfanilamide as a prophylactic measure in recurrent rheumatic infection. A controlled study involving 131 "patient-seasons," 483
Fels, S., *see* Shay, H., 550
Felsenfeld, O., Yeast-like fungi in the intestinal tract of chronically institutionalized patients, 60
Fever induced by typhoid vaccine and malaria in patients with neurosyphilis, Electroencephalographic studies during, 512

Fibrinogen in a rapid method of determining cell volume, The use of, 29
Figueiró, Dr. José Maria, *see* Versiani, Dr. Oscar, 161
Finland, Maxwell, *see* Peterson, Osler L., 166
Fletcher, A., *see* Koop, C., 415
Flippin, H., *see* Reinhold, J., 413
Floyd, N., *see* Weinhouse, S., 812
Foster, W., *see* McClendon, J., 549
Freireich, A., *see* Koffler, A., 374
Fried, S., *see* Bigg, E., 361
Fried, S., *see* Bigg, E., 370
Fungi in the intestinal tract of chronically institutionalized patients, Yeast-like, 60

G

Gargoylism. Review of literature with report of 2 cases, 184
Geever, E., The pathologic changes in sulfadiazine intoxication, 331
Gelatin as a plasma substitute, Some clinical experience with, 415
Gelatin preparations in repeated massive hemorrhage and infusion, Tests of pyrogenicity, antigenicity, and the efficacy of ossein, 414
Getting, V., Tropical disease and global war, 404
Glucose in experimental deficiency, VII. Blood pyruvate and lactate-pyruvate ratio following the ingestion of. Studies of the B vitamins in the human subject, 247
Glycol and triethylene glycol in liquid and vapor form, Inflammability characteristics of propylene, 370
vapors for bacterial control in large spaces, The use of, 361
Gold salts in the treatment of rheumatoid arthritis, Analysis of results obtained with small doses of, 528
Gonadotropin in male infertility. An analysis of 127 patients, The use of equine, 519
Gore, I., *see* Colvin, S., 378
Granuloma of bone," Hand-Schüller-Christian's syndrome and "eosinophilic or solitary, 161
Graves' disease with special reference to its ophthalmic component, The nature of, 1
Gray, S., The use of fibrinogen in a rapid method of determining cell volume, 29
Green, M., *see* Sevag, M., 686
Greenblatt, M., Rose, A., Electroencephalographic studies during fever induced by typhoid vaccine and malaria in patients with neurosyphilis, 512
Grimes, E., *see* Thompson, C., 342
Gross, Sidney, *see* Wilhelm, Seymour F., 196
Gruskin, B., *see* Rawls, W., 528
Guadalcanal. I. Persistent symptoms in 3 cases, Neuropsychiatric casualties from, 770

H

Hand-Schüller-Christian's syndrome and "eosinophilic or solitary granuloma of bone," 161
Hanson, J., *see* Logue, R., 765
Harrell, G., *see* Horne, S., 759
Harrison, T., Clinical aspects of pain in the chest. 1. Angina pectoris, 561
Haugaard, N., *see* Stadie, W. C., 84
Haydak, Mykola H., Vivino, A. Earl, Boehrer, John J., Bjorndahl, Oscar, Palmer, Leroy S., A clinical and biochemical study of cow's milk and honey as an essentially exclusive diet for adult humans, 209
Heart block. A study of 100 cases with prolonged P-R interval, 765
Heart disease in Selective Service examinees. A study of 20,000 examinees in the Pacific Northwest, 204
"Heat resistance" of erythrocytes. A specific test for the recognition of Marchiafava's anemia, The, 624
Hegglin, R., Maier, C., The "heat resistance" of erythrocytes. A specific test for the recognition of Marchiafava's anemia, 624
Heilman, D., A method for standardizing penicillin, 477
Heinle, R., Weir, D., Morphologic Obliteration of chronic myeloid leukemia by active tuberculosis. Report of a case, 450
Hemophilic plasmas, Observations on the anticephalin activity of normal and, 814
Hemorrhage and infusion, Tests of pyrogenicity, antigenicity, and the efficacy of ossein gelatin preparations in repeated massive, 414
Henle, G., *see* Henle, W., 705
Henle, W., Henle, G., Interference between inactive and active viruses of influenza. I. The incidental occurrence and artificial induction of the phenomenon, 705
Henle, W., Henle, G., Interference between inactive and active viruses of influenza. II. Factors influencing the phenomenon, 717
Hepatorenal failure in the Waterhouse-Friderichsen syndrome. Clinico-pathologic observations in 2 cases with prolonged survival periods, 385
Higgins, G. M., The relation of vitamin B to the toxicity of promin as tested by the self-selection method, 239
Hiller, G., Johnson, R., Abdominal aortic aneurysm. Rupture into the jejunum preceded by occult blood in the stool, 600
Hinshaw, H., *see* Feldman, W., 290
Histoplasmosis (Darling) with autopsy, A case of, 378
Histoplasmosis in an infant with autopsy, A case of, 230

Honey as an essentially exclusive diet for adult humans, A clinical and biochemical study of cow's milk and, 209
Horne, S., and Harrell, G., Trichinella skin tests in patients in general hospitals and tuberculosis sanatoria, 759
Hyperglobulinemia, Relationship of lymphogranuloma venereum infection to the incidence of, 643
Hypertension, Obstructive lesions of the main renal artery in relation to, 394
Hypoprothrombinemia, Idiopathic, 77

I

Imber, I., A tumor occurring in the superior pulmonary sulcus, 654
Immunity, in its production. Insulin resistance. The rôle of, 354
Infarction of the lateral wall of the left ventricle. Pathologic and electrocardiographic study, 588
Infertility. An analysis of 127 patients, The use of equine gonadotropin in male, 519
Influenza, Experimental human, 306
Influenza. I. The distribution of inhaled material, The inhalatory route for prophylaxis and treatment of experimental, 40
Influenza. I. The incidental occurrence and artificial induction of the phenomenon, Interference between inactive and active, 705
II. Immune serum in prophylaxis and treatment, 47
Ingraham, N., *see* Stokes, J., 540
Inhalatory route for prophylaxis and treatment of experimental influenza. I. The distribution of inhaled material, The, 40
Insecticide penetration, Insect nerve sheaths and, 267
Institutionalized patients, Yeast-like fungi in the intestinal tract of chronically, 60
Insulin resistance. The rôle of immunity in its production, 354
Tumefaction of subcutaneous fat following the injection of, 776
Interference between inactive and active viruses of influenza. I. The incidental occurrence and artificial induction of the phenomenon, 705
Interference between inactive and active viruses of influenza. II. Factors influencing the phenomenon, 717
Intestinal tract of chronically institutionalized patients, Yeast-like fungi in the, 60
Iodine in erythrocytes and plasma and elsewhere, Protein-bound, 549
Ion adsorption, Determination of serum total base by, 129

J

Jaundice. A review of the literature and report of a case, Homologous serum, 626
Jennings, B., *see* Bigg, E., 361
Jennings, B., *see* Bigg, E., 370
Johnson, R., *see* Hiller, G., 600
Junqueira, Dr. Moacyr A., *see* Versiani, Dr. Oscar, 161

K

Kaplan, I., One year observations of the treatment of cancer with avidin (egg white), 733
Kay, G., *see* Williams, R., 701
Kennedy, W., Lukens, F., Alloxan diabetes, 550
Ketone body formation from fatty acids, using heavy carbon as a tracer, 812
Kety, S., *see* Schmidt, C., 813
Klein, C., *see* Saland, G., 749
Klein, D., Elsom, K. O., Studies of the B vitamins in the human subject. VII. Blood pyruvate and lactate-pyruvate ratio following the ingestion of glucose in experimental deficiency, 247
Koffler, A., Freireich, A., Thrombophlebitis as a hitherto unreported complication of thiocyanate therapy of hypertension, 374
Koletsky, S., Barnebee, J., "Cardiac" or congestive cirrhosis. Pathologic and clinical aspects, 421
Komarov, S., *see* Shay, H., 550
Koop, C., Fletcher, A., Riegel, C., Some clinical experience with gelatin as a plasma substitute, 415

L

Labyrinth, Depressor effect of cold upon the static receptors of the, 815
Lepper, M., *see* Dowling, H., 349
Lerman, J., Insulin resistance. The rôle of immunity in its production, 354
Leukemia by active tuberculosis. Morphologic obliteration of chronic myeloid, 450
Osteosclerosis, myelofibrosis and, 141
Levy, Sol., *see* Lurie, Louis A., 184
Lloyd, P., Acute thrombocytopenic purpura in infectious mononucleosis. Report of a case, 620
Logue, R., and Hanson, J., Heart Block. A study of 100 cases with prolonged P-R interval, 765
Lubin, A. J., Recent contributions to neurology from war experiences, 114
Lukens, F., *see* Kennedy, W., 550
"Lupus erythematosus" concept: An attempt at integration, The, 540
Lurie, Louis A., Levy, Sol., Gargoylism. Review of literature with report of two cases, 184
Lymphocytes and symptoms suggesting the recovery phase of infectious mononucleosis, Blood studies in allergy. II. The presence in allergic disease of atypical, 638

Lymphogranuloma venereum infection to the incidence of hyperglobulinemia, Relationship of, 643
Lynch, H., *see* Chapple, C., 488
Lyons, Wm. R., *see* Personnel of Naval Laboratory Research Unit No. 1, 40

M

Maier, C., *see* Hegglin, R., 624
Malm, M., *see* Nylin, G., 743
Marangoni, B., D'Agati, V., Hepatorenal failure in the Waterhouse-Friderichsen syndrome. Clinico-pathologic observations in 2 cases with prolonged survival periods, 385
Marangoni, B., D'Agati, V., Treatment of 134 cases of meningococcic infection with massive doses of sulfadiazine, 67
Marchiafava's anemia, The "heat resistance" of erythrocytes. A specific test for the recognition of, 624
Master, A., in collaboration with Nuzie, S., Brown, R., Parker, R., The electrocardiogram and the "two-step" exercise. A test of cardiac function and coronary insufficiency, 435
McClendon, J., Foster, W., Protein-bound iodine in erythrocytes and plasma and elsewhere, 549
Means, J. H., The nature of Graves' disease with special reference to its ophthalmic component, 1
Medes, G., *see* Weinhouse, S., 812
Meningitis caused by Neisseria perflava, A case of acute, 376
Meningococcic infection with massive doses of sulfadiazine, Treatment of 134 cases of, 67
meningitis and meningococcemia, Sulfadiazine and its sodium compound in treatment of, 492
Mercurial diuretics, Prevention of absorption and of convulsions by, 812
Metabolic rate, The chief urinary pigment. The relationship between the rate of excretion of the yellow urinary pigment and the, 507
Method of determining cell volume, The use of fibrinogen in a rapid, 29
Milk and honey as an essentially exclusive diet for adult humans, A clinical and biochemical study of cow's, 209
Miller, E., *see* Beeson, P., 643
Miller, T., *see* Neefe, J., 626
Monkey's brain *in vivo*, The oxygen metabolism of the, 813
Mononucleosis. Report of a case, Acute thrombocytopenic purpura in infectious, 620
Moses, H., *see* Feldman, W., 290
Motility patterns of the child's digestive tract: A review, Major, 782
Mudd, S., Clues regarding the organization of the simplest living systems, 130
Mumps and mumps pancreatitis, Blood diastase values in, 461
Murphy, F. D., Clark, J. K., Idiopathic hypoprothrombinemia, 77
Muscles (effects of stimulation, rigor, drugs), Roentgen ray diffraction patterns of striated, 266
Myelofibrosis and leukemia, Osteosclerosis, 141

N

Naide, M., with the technical assistance of Saÿen, A., A test for vascular tone in humans and its application to the study of vascular diseases with special reference to the etiology and prevention of thrombophlebitis, 606
Nasopharynx, Carcinoma of the, 342
Naval Laboratory Research Unit No. 1, Personnel of, Experimental Human Influenza, 306
Neefe, J., Miller, T., Chornock, F., Homologous serum jaundice. A review of the literature and report of a case, 626
Neisseria perflava, A case of acute meningitis caused by, 376
Nelson, J., *see* Applebaum, E., 492
Nerve sheaths and insecticide penetration, Insect, 267
Neurology from war experiences, Recent contributions to, 114
Neuropsychiatric casualties from Guadalcanal. I. Persistent symptoms in 3 cases, 770
Neurosyphilis, Electroencephalographic studies during fever induced by typhoid vaccine and malaria in patients with, 512
Nutrition in preoperative and postoperative care, The rôle of. A review, 253
Nuzie, S., *see* Master, A., 435
Nylin, G., Malm, M., Concentration of red blood corpuscles containing labeled phosphorus compounds in the arterial blood after the intravenous injection, 743

O

Obstetrics, Analgesia in, 804
Ophthalmic component, The nature of Graves' disease with special reference to its, 1
Organization of the simplest living systems, Clues regarding the, 130
Osteosclerosis, myelofibrosis and leukemia, 141
Ostow, M., Philo, S., The chief urinary pigment. The relationship between the rate of excretion of the yellow urinary pigment and the metabolic rate, 507
Oxygen metabolism of the monkey's brain *in vivo*, The, 813
Oxygen poisoning, 84

P

Pain in the chest. 1. Angina pectoris, Clinical aspects of, 561

Palmer, L. S., *see* Haydak, M., 209
Pancreas, A tabulation of the recent literature and report of a case, Annular, 430
Pancreatic function tests in 47 surgically treated cases, The diagnostic value of, 281
Pancreatitis, Blood diastase values in mumps and mumps, 461
Paravertebral block in peripheral vascular disease, The evaluation of alcohol lumbar, 749
Parker, R., *see* Master, A., 435
Parkins, W., Saxe, L., Vars, H., Tests of pyrogenicity, antigenicity, and the efficacy of ossein gelatin preparations in repeated massive hemorrhage and infusion, 414
Penicillin, A method for standardizing, 477
A review of the literature through 1943, 661
Studies on bioassay of, 267
Pennes, H., *see* Schmidt, C., 813
Personnel of Naval Laboratory Research Unit No. 1, Wm. R. Lyons, The inhalatory route for prophylaxis and treatment of experimental influenza. I. The distribution of inhaled material, 40
Personnel of Naval Laboratory Research Unit No. 1, II. Immune Serum in Prophylaxis and Treatment, 47
Peters, M., *see* Colvin, S., 378
Peterson, Osler L., Finland, Maxwell, Barnes, Mildred W., Wilcox, Clare, Sulfonamide inhibiting action of procaine, 166
Philo, S., *see* Ostow, M., 507
Phosphorus compounds in the arterial blood after the intravenous injection, Concentration of red blood corpuscles containing labeled, 743
Physicochemical blood tests in sickle cell anemia, Diagnostic, 152
Physiology of air-borne infection, An apparatus for study of the, 131
Plasma substitute, Some clinical experience with gelatine as a, 415
Plummer, Norman, Wheeler, Charles, The toxicity of sulfadiazine. Observations on 1357 cases, 175
Poisoning, Oxygen, 84
Polis, B. D., Reinhold, J. G., Determination of serum total base by ion adsorption, 129
Pollack, L., *see* Reinhold, J., 413
Popper, H., *see* Steigmann, F., 468
Procaine, Sulfonamide inhibiting action of, 166
Promin as tested by the self-selection method, The relation of vitamin B to the toxicity of, 239
Prothrombin, The use of horse brain thromboplastin for the quantitative determination of, 268
Pulmonary sulcus, A tumor occurring in the superior, 654
Pyruvate and lactate-pyruvate ratio following the ingestion of glucose in experimental deficiency, VII. Blood. Studies of the B vitamins in the human subject, 247

R

Randolph, T., Gibson, E., Blood studies in allergy. II. The presence in allergic disease of atypical lymphocytes and symptoms suggesting the recovery phase of infectious mononucleosis, 638
Rasberry, E., *see* Diaz-Rivera, R., 754
Rawls, W., Gruskin, B., Ressa, A., Dworzan, H., and Schreiber, D., Analysis of results obtained with small doses of gold salts in the treatment of rheumatoid arthritis, 528
Red blood corpuscles containing labeled phosphorus compounds in the arterial blood after the intravenous injection, Concentration of, 743
Reinhold, J., Flippin, H., Domm, A., Pollack, L., "Bound" sulfonamide compounds in plasma with special reference to renal clearance of various sulfonamides, 413
Renal artery in relation to hypertension, Obstructive lesions of the main, 394
clearance of various sulfonamides, "Bound" sulfonamide compounds in plasma with special reference to, 413
Ressa, A., *see* Rawls, W., 528
Results obtained with small doses of gold salts in the treatment of rheumatoid arthritis, Analysis of, 528
Retina, Senile changes in the choroid and, 258
Reviews (Reviewer's initials in parentheses):
Ackerman, L., Health and Hygiene (H. B.), 691
Arnow, L. E., Introduction to Physiological and Pathological Chemistry (H. V.), 276
Bacon, H. E., Essentials of Proctology (L. T.), 136
Bailey, H., Pye's Surgical Handicraft (H. Z.), 274
Ballard, J. F., Catalogue of the Medieval and Renaissance Manuscripts and Incunabula in the Boston Medical Library (E. K.), 557
Bargen, J. A., The Modern Management of Colitis (L. LaT), 689
Bart, Sir, H. R., The British Encyclopedia of Medical Practice (E. K.), 555
Bell, E. T., A Text-book of Pathology (D. C.), 820
Bercovitz, Z. T., Clinical Tropical Medicine (H. S.), 695
Berliner, M. L., Biomicroscopy of the Eye (F. A.), 694
Berman, L., Behind the Universe (N. Y.), 698
Bert, P., Barometric Pressure. Researches in Experimental Physiology (B. R.), 133
Bloor, W. R., Biochemistry of the Fatty Acids and Their Compounds, the Lipids (H. V.), 278
Bourne, G. (edited by), Cytology and Cell Physiology (D. C.), 135
Cattell, J., and Hoerr, N., Biological Symposia (J. C.), 692
Cecil, R. L., A Textbook of Medicine (E. K.), 269

Reviews (Reviewer's initials in parentheses):

Chamberlain, E. N., Symptoms and Signs in Clinical Medicine (J. S.), 416
Cowdry, E. V., Microscopic Technique in Biology and Medicine (F. E.), 271
Crabtree, E. G., Urological Diseases of Pregnancy (L. LaT.), 278
Cummins, H., Finger Prints, Palms and Soles (R. W.), 269
Curren, D., Psychological Medicine (N. Y.), 277
Davis, J. E., Principles and Practice of Rehabilitation (N. Y.), 273
Davson, H., Danielli, J. F., and Harvey, E. N., The Permeability of Natural Membranes (H. V.), 696
DeKruif, P., Kaiser Wakes the Doctors (J. L.), 137
DeLorimier, A. A., The Arthropathies. A Handbook of Roentgen Diagnosis (E. P.), 556
Draper, G., Dupertuis, C., and Caughey, J., Human Constitution in Clinical Medicine (R. B.), 818
Dunbar, F. D., Psychosomatic Diagnosis (D. P.), 688
Edelstein, L., The Hippocratic Oath (E. K.), 817
Files, G. W., Medical Radiographic Technic (E. P.), 553
First National Congress on Endemo-epidemic Diseases, held at the "Instituto Jose Penna," School of Medical Sciences of Buenos Aires, Nov., 1942, Primer Congreso Nacional Sobre Enfermedades Endemo-Epidemicas (L. G.), 692
Forbus, W. D., Reaction to Injury. Pathology for Students of Disease Based on the Functional and Morphological Responses of Tissues to Injurious Agents (W. S.), 272
Fulton, J. F., Physiology of the Nervous System (J. C.), 270
Garrison, F. H., A Medical Bibliography (E. K.), 274
Gershenfeld, L., Urine and Urinalysis (L. LaT.), 272
Glasser, O., Medical Physics (E. K.), 697
Greenwood, M., Authority in Medicine (E. K.), 819
Haagensen, C. D., and Lloyd, W. E., A Hundred Years of Medicine (E. K.), 554
Ham, A. W., Doctor in the Making. The Art of Being a Medical Student (E. K.), 271
Heilbrunn, L. V., An Outline of General Physiology (M. J.), 697
Hughes, W. L., Reconstructive Surgery of the Eyelids (F. A.), 137
Jenkins, G. L., and Hartung, W. H., The Chemistry of Organic Medicinal Products (H. V.), 696
Jenkins, G. L., Quantitative Pharmaceutical Chemistry (J. C.), 693
Jessee, R. W., Self-teaching Tests in Arithmetic for Nurses (H. F.), 135
Kaufman, W., The Common Form of Niacin Amide Deficiency Disease. Aniacinamidosis (E. W.), 269
Kolmer, J., Clinical Diagnosis by Laboratory Examinations (E. K.), 816
Lake, N. C., The Foot (P. C.), 416
Levinson, A., Pioneers of Pediatrics (E. K.), 690
Lewin, P., Backache and Sciatic Neuritis (P. C.), 694
Lewis, G. M., An Introduction to Medical Mycology (F. W.), 136
Lichtwitz, L., Pathology and Therapy of Rheumatic Fever (P. P.), 689
Lowsley, A., Collaborators: Hinman, F., Smith, D., Gutierrez, R., The Sexual Glands of the Male (L. LaT.), 818
Lowsley, O. S., Urology for Nurses (L. LaT.), 555
McCready, B. W., Miller, G., On the Influence of Trades, Professions, and Occupations in the United States, in the Production of Disease (E. K.), 694
McGregor, A. L., A Synopsis of Surgical Anatomy (J. L.), 695
Manson-Bahr, Sir Philip, The Dysenteric Disorders (E. R.), 275
Medical Clinics of North America, Symposium on Medical Emergencies on the Home Front (F. M.), 554
Morgan, C. T., Physiological Psychology (J. S.), 417
Nauss, R. W., Medical Parasitology and Zoölogy (H. R.), 690
New York Academy of Medicine Lectures to the Laity, The March of Medicine (E. K.), 691
Oberling, C., The Riddle of Cancer (D. C.), 819
Ogilvie, R. F., Pathological Histology (I. Z.), 417
Page, I. H., Hypertension—A Manual for Patients with High Blood Pressure (D. C.), 134
Pagel, W., The Religious and Philosophical Aspects of Van Helmont's Science and Medicine (E. K.), 817
Remich, A. E., Electronic Interpretations of Organic Chemistry (S. G.), 554
Report of the Association for Research in Nervous and Mental Disease. Editorial Board: Harold G. Wolff, Chairman; Herbert S. Gasser, and J. C. Hinsey. Pain. XXIII. (N. Y.), 275
Salter, A., What is Hypnosis (N. Y.), 817
Schmidt, C. L. A., Addendum to the Chemistry of the Amino Acids and Proteins (J. J.), 273
Shapiro, H. H., Applied Anatomy of the Head and Neck. For Students and Practioners of Dentistry (L. C.), 135
Snapper, I., Medical Clinics on Bone Diseases. A Text and Atlas (P. C.), 270
Swartz, J. H., Elements of Medical Mycology (H. M.), 277
Thorek, M., A Surgeon's World (H. S.), 817
Thorpe, W. V., Biochemistry for Medical Students (H. V.), 277
Tobias, N., Essentials of Dermatology (H. B.), 691
Turner, C. E., Personal and Community Health (F. E.), 418
Winslow, C. E. A., The Conquest of Epidemic Disease. A Chapter in the History of Ideas (W. W.), 270
Worthing, A. G., Treatment of Experimental Data (D. D.), 276

Rheumatic infection. A controlled study involving 131 "patient-seasons," Sulfanilamide as a prophylactic measure in recurrent, 483
Rheumatoid arthritis, Analysis of results obtained with small doses of gold salts in the treatment of, 528
Rhinitis, Vasomotor, 534
Riegel, C., *see* Koop, C., 415
Riggs, B. C., *see* Stadie, W. C., 84
Roentgen ray diffraction patterns of striated muscles (effects of stimulation, rigor, drugs), 266
Rose, A., *see* Greenblatt, M., 512
Rosner, A., Neuropsychiatric casualties from Guadalcanal. I. Persistent symptoms in 3 cases, 770

S

Saland, G., and Klein, C., The evaluation of alcohol lumbar paravertebral block in peripheral vascular disease, 749

Saÿen, A., *see* Naide, M., 606
Saxe, L., *see* Parkins, W., 414
Schiff, L., Shapiro, N., and Stevens, R., Observations on the oral administration of citrated blood in man. III The effect on temperature and the white blood cell count, 465
Schlumberger, H. G., Service, A. C., A case of histoplasmosis in an infant with autopsy, 230
Schmidt, C., Pennes, H., and Kety, S., The oxygen metabolism of the monkey's brain *in vivo*, 813
Schmitt, G., Penicillin. A review of the literature through 1943, 661
Schneeberg, N. G., *see* Trasoff, A., 63
Schreiber, D., *see* Rawls, W., 528
Selective Service examinees, Heart disease in. A study of 20,000 examinees in the Pacific Northwest, 204
Senile changes in the choroid and retina, 258
Serum jaundice, A review of the literature and report of a case, Homologous, 626
proteins (Formula for calculating serum protein concentration), A rapid method for estimating, 685
Service, A. C., *see* Schlumberger, H. G., 230
Sevag, M., Green, M., The metabolism of tryptophane by *Staphylococcus aureus* as a critical factor in relation to the mode of action of sulfonamides, 686
Shapiro, N., *see* Schiff, L., 465
Shay, H., Komarov, S., Siplet, H., Fels, S., Excretion of certain newer sulfonamides in the bile and urine, 550
Shipley, R. A., Treatment of Addison's disease with pellets of desoxycorticosterone acetate, 19
Sickle cell anemia, Diagnostic physicochemical blood tests in, 152
Siplet, H., *see* Shay, H., 550
Skin measured on the fingers, Electrical potential of human, 550
Smith, L., Chlorophyll: An experimental study of its water-soluble derivatives. 1. Remarks upon the history, chemistry, toxicity and antibacterial properties of water-soluble chlorophyll derivatives as therapeutic agents, 647
Sophian, L., A case of acute meningitis caused by *Neisseria perflava*, 376
Spiegel, E., Depressor effect of cold upon the static receptors of the labyrinth, 815
Stadie, W. C., Riggs, B. C., Haugaard, N., Oxygen Poisoning, 84
Staphylococcus aureus as a critical factor in relation to the mode of action of sulfonamides, The metabolism of tryptophane by, 686
Steigmann, F., Popper, H., The influence of large doses of vitamin A upon the plasma vitamin A level, 468
Stemmerman, M. G., *see* Auerbach, O., 219
Stevens, R., *see* Schiff, L., 465
Stines, P., *see* Bauman, L., 281
Stofer, B., Annular pancreas. A tabulation of the recent literature and report of a case, 430
Stokes, J., Beerman, H., and Ingraham, N., The "lupus erythematosus" concept: An attempt at integration, 540
Sulfadiazine, The toxicity of. Observations on 1357 cases, 175
Sulfadiazine and its sodium compound in treatment of meningococcic meningitis and meningococcemia, 492
Sulfadiazine intoxication, The pathologic changes in, 331
Sulfadiazine, Treatment of 134 cases of meningococcic infection with massive doses of, 67
Sulfanilamide as a prophylactic measure in recurrent rheumatic infection. A controlled study involving 131 "patient-seasons," 483
Sulfathiazole, sulfadiazine, and sulfapyridine, "Drug Fever" accompanying second courses of, 349
Sulfocyanates and their relation to blood pressure, The naturally occurring blood, 63
Sulfonamide aerosol inhalation. A supplemental note, A study of, 488
compounds in plasma with special reference to renal clearance of various sulfonamides, "Bound," 413
inhibiting action of procaine, 166
Sulfonamides in the bile and urine, Excretion of certain newer, 550
The metabolism of tryptophane by *Staphylococcus aureus* as a critical factor in relation to the mode of action of, 686
Sunderman, F., A rapid method for estimating serum proteins (Formula for calculating serum protein concentration), 685
Syphilis, Electrocardiographic patterns in cardiovascular, 317
Systems, Clues regarding the organization of the simplest living, 130

T

Tanner, J., Intercorrelations between cardiovascular variables in healthy men, and the relation of physique to these and other variables, 684
Therapeutic agents, Chlorophyll: An experimental study of its water-soluble derivatives. I. Remarks upon the history, chemistry, toxicity and antibacterial properties of water-soluble chlorophyll derivatives as, 647
Thiocyanate therapy of hypertension, Thrombophlebitis as a hitherto unreported complication of, 374

Thiouracil storage in the thyroid as affected by thyrotropic hormone and potassium iodide, 701
Thoma, K. H., Oral pathology, 693
Thompson, C., Grimes, E., Carcinoma of the nasopharynx, 342
Thomson, H., Feil, H., Infarction of the lateral wall of the left ventricle. Pathologic and electrocardiographic study, 588
Thrombocytopenic purpura in infectious mononucleosis. Report of a case, Acute, 620
Thrombophlebitis, A test for vascular tone in humans and its application to the study of vascular diseases with special reference to the etiology and prevention of, 606
as a hitherto unreported complication of thiocyanate therapy of hypertension, 374
Thromboplastin for the quantitative determination of prothrombin, The use of horse brain, 268
Thyroid as affected by thyrotropic hormone and potassium iodide, Thiouracil storage in the, 701
Tocantins, L., Observations on the anticephalin activity of normal and hemophilic plasmas, 814
Trasoff, A., Schneeberg, N. G., The naturally occurring blood sulfocyanates and their relation to blood pressure, 63
Treatment of Addison's disease with pellets of desoxycorticosterone acetate, 19
of experimental influenza. I. The distribution of inhaled material, The inhalatory route for prophylaxis and, 40. II. Immune serum in prophylaxis and treatment, 47
of 134 cases of meningococcic infection with massive doses of sulfadiazine, 67
Trichinella skin tests in patients in general hospitals and tuberculosis sanatoria, 759
Tropical disease and global war, 404
Tryptophane by *Staphylococcus aureus* as a critical factor in relation to the mode of action of sulfonamides, The metabolism of, 686
Tuberculosis in congenital heart disease, The development of pulmonary, 219
of 4,4′-diaminodiphenylsulfone, The effects on experimental, 290
Morphologic obliteration of chronic myeloid leukemia by active, 450
Tumor occurring in the superior pulmonary sulcus, A, 654
"Two-step" exercise, Electrocardiogram and the. A test of cardiac function and coronary insufficiency, The, 435

U

Urinary pigment. The relationship between the rate of excretion of the yellow urinary pigment and the metabolic rate, The chief, 507

V

Vascular disease, The evaluation of alcohol lumbar paravertebral block in peripheral, 749
tone in humans and its application to the study of vascular diseases with special reference to the etiology and prevention of thrombophlebitis, A test for, 606
Ventricle. Pathologic and electrocardiographic study, Infarction of the lateral wall of the left, 588
Versiani, Dr. Oscar, Figueiró, Dr. José Maria, Junqueira, Dr. Moacyr A., Hand-Schüller-Christian's syndrome and "eosinophilic or solitary granuloma of bone," 161
Vitamin A upon the plasma vitamin A level, The influence of large doses of, 468
Vitamin B to the toxicity of promin as tested by the self-selection method, The relation of, 239
Vivino, A. Earl, *see* Haydak, Mykola, 209

W

Wachstein, Max, *see* Churg, Jacob, 141
Wagener, H. P., Senile changes in the choroid and retina, 258
Walzl, E., *see* Woolsey, C., 685
War experiences, Recent contributions to neurology from, 114
Tropical disease and global, 404
Waterhouse-Friderichsen syndrome. Clinico-pathologic observations in 2 cases with prolonged survival periods, Hepatorenal failure in the, 385
Weber, H., A new cholecystographic medium, 678
Weinglass, A., *see* Williams, R., 701
Weinhouse, S., Medes, G., and Floyd, N., Ketone body formation from fatty acids, using heavy carbon as a tracer, 812
Weir, D., *see* Heinle, R., 450
Wells, W. F., An apparatus for study of the physiology of air-borne infection, 131
Wheeler, Charles, *see* Plummer, Norman, 175
Whipple, A., *see* Bauman, L., 281
Wilburne, Morris, Ceccolini, Edward M., Heart disease in Selective Service examinees. A study of 20,000 examinees in the Pacific Northwest, 204
Wilcox, Clare, *see* Peterson, Osler L., 166

Wilhelm, Seymour F., Gross, Sidney, Surgical removal of adrenal adenoma with relief of Cushing syndrome, 196
Williams, R., Weinglass, A., Kay, G., Thiouracil storage in the thyroid as affected by thyrotropic hormone and potassium iodide, 701
Winsor, Travis, Burch, G. E., Diagnostic physicochemical blood tests in sickle-cell anemia, 152
Wolman, I., Major motility patterns of the child's digestive tract: A review, 782
Woolsey, C., Walzl, E., Topical projection of the cochlea to the cerebral cortex of the monkey, 685

Y

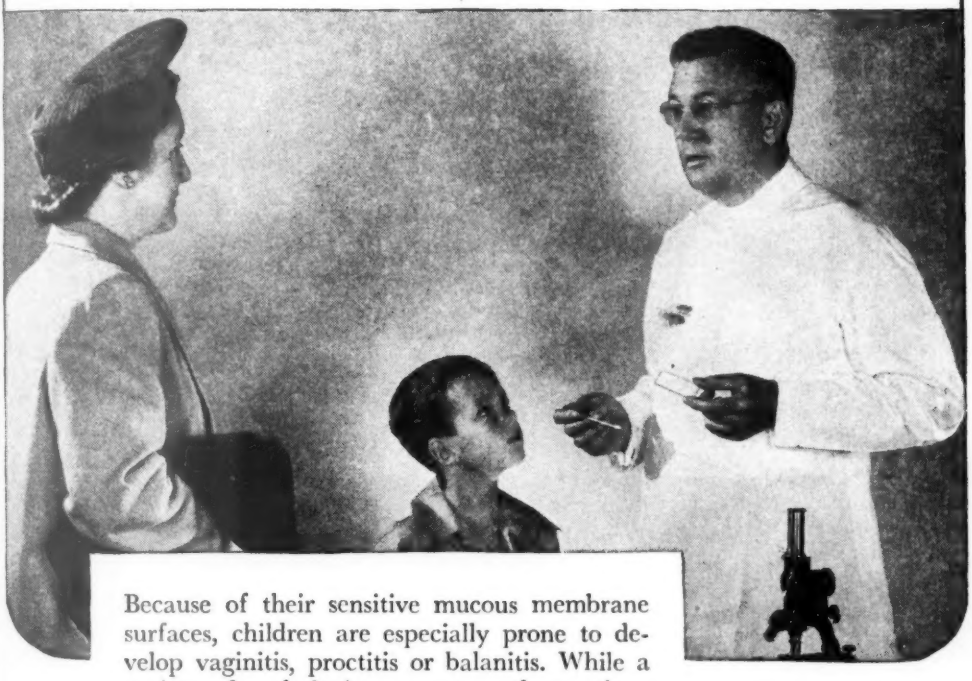
Yuile, C., Obstructive lesions of the main renal artery in relation to hypertension, 394

Z

Zelman, S., Blood diastase values in mumps and mumps pancreatitis, 461

IN

IN THE ORIFICIAL PRURITUS OF *Children*



Because of their sensitive mucous membrane surfaces, children are especially prone to develop vaginitis, proctitis or balanitis. While a variety of pathologic processes and organisms may contribute, the lesions have one common characteristic—severe itching. The scratching which invariably ensues, produces secondary traumatic lesions with their threat of superimposed infection. Because children cannot be expected to suppress the desire to scratch, dependable anti-pruritic medication is required. For this purpose, the efficacy of Calmitol Ointment is long demonstrated. It dependably stops itching, regardless of cause. Its action is sustained, requiring only infrequent application. Calmitol Ointment contains no irritating substances, and therefore may be applied safely to all external surfaces of infants and children.

Thos. Leeming & Co. Inc.

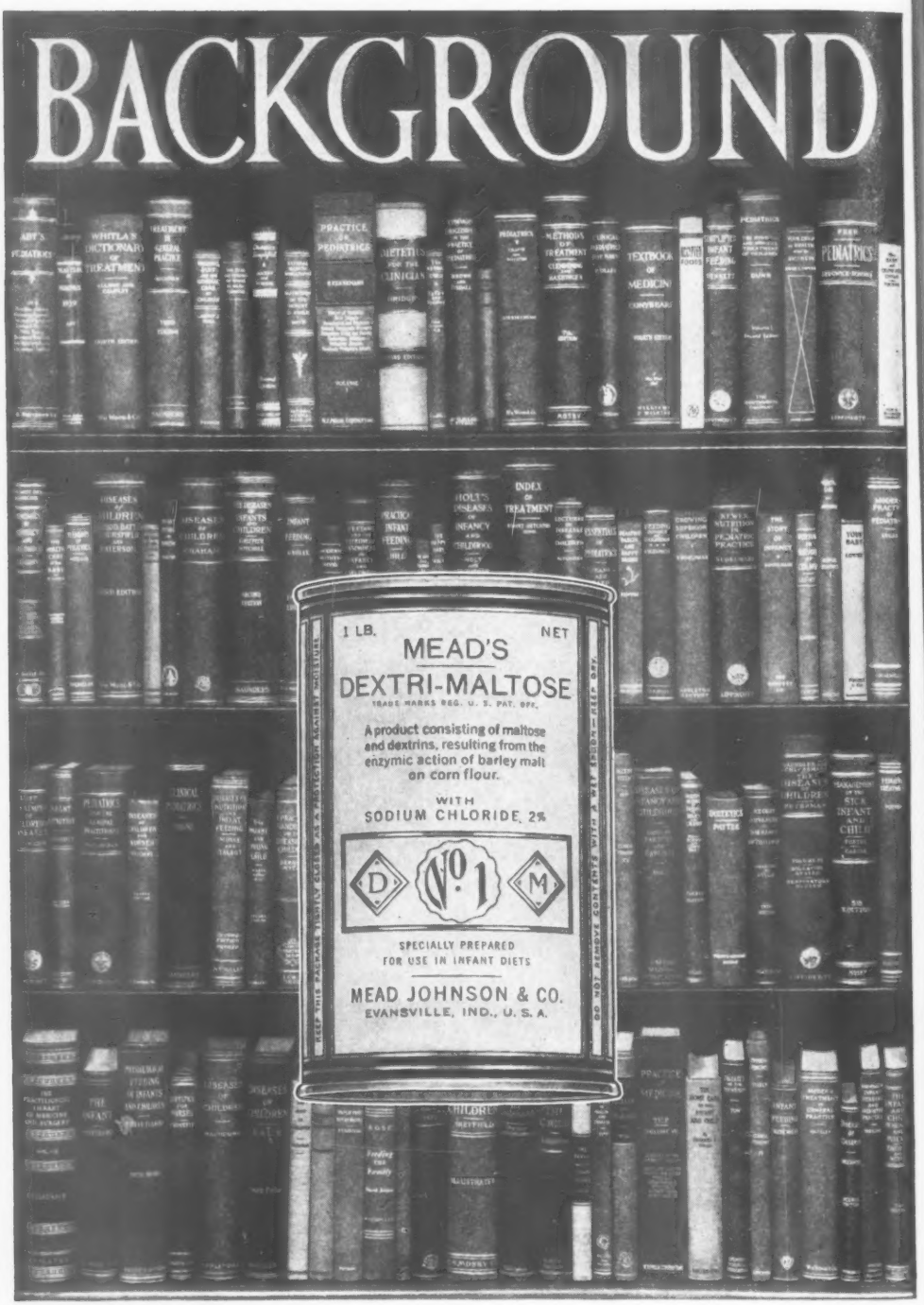
155 East 44th Street • New York 17, N. Y.

The anti-pruritic properties of Calmitol are due to the valuable pharmacodynamic influence of its ingredients: camphorated chloral, menthol, and hyoscyamine oleate, in an alcohol-chloroform-ether vehicle. A three-fold action is exerted: (1) Sensory impulses are blocked at the afferent nerve endings and cutaneous receptor organs; (2) local active hyperemia encourages resolution of the underlying process; (3) bacteriostasis aids in preventing spread. Calmitol Ointment is thoroughly bland and may safely be applied to infants' skin. * * * Professional samples on request.

CALMITOL

THE DEPENDABLE ANTI-PRURITIC

BACKGROUND



THE use of cow's milk, water and carbohydrate mixtures represents the one system of infant feeding that consistently, for three decades, has received universal pediatric recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Mead's Dextri-Maltose.

e
as
is
of